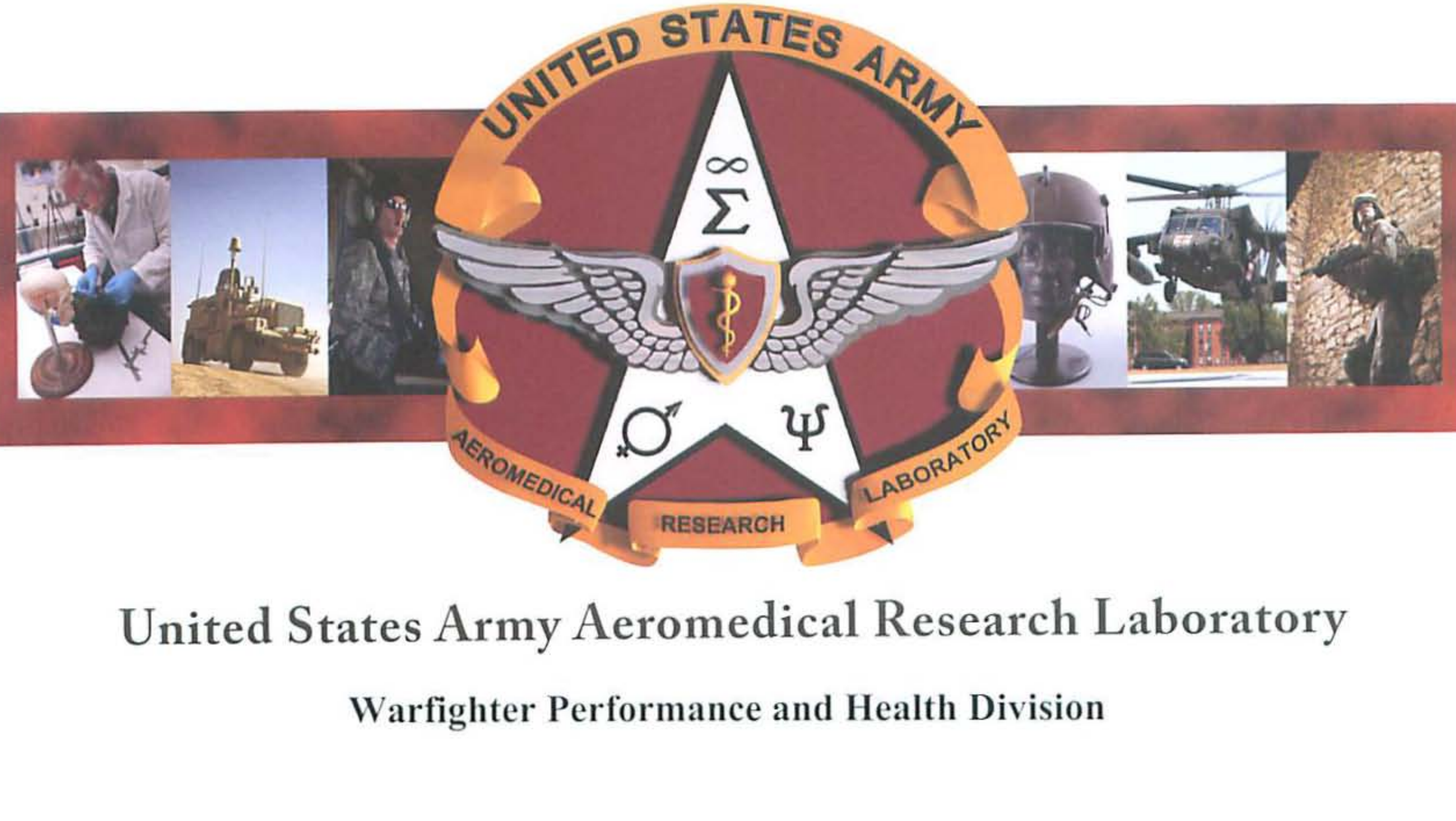
USAARL Report No. 2010-17

Comparison of the Effects of Ketamine and Morphine on the Performance of Representative Military Tasks

By Steven J. Gaydos, Amanda M. Kelley,
Catherine M. Webb, Jeremy R. Athy,
Patricia L. Walters, Bradley S. Erickson,
Melody R. King, David Lopez, Pedro A. Cruz,
Robert M. Wildzunas, Arthur Estrada



United States Army Aeromedical Research Laboratory

Warfighter Performance and Health Division

August 2010

Approved for public release, distribution unlimited.

Human use

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRMC Reg 70-25 on Use of Volunteers in Research.

REPORT DOCUMENTATION PAGE					*Form Approved* *OMB No. 0704-0188*

1. REPORT DATE *(DD-MM-YYYY)*: 01-09-2010

2. REPORT TYPE: Final

3. DATES COVERED *(From - To)*:

4. TITLE AND SUBTITLE
Comparison of the Effects of Ketamine and Morphine on the Performance of Representative Military Tasks

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Steven J. Gaydos, Amanda M. Kelley, Catherine M. Webb, Jeremy R. Athy, Patricia L. Walters, Bradley S. Erickson, Melody R. King, David Lopez, Pedro A. Cruz, Robert M. Wildzunas, and Arthur Estrada

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
U.S. Army Aeromedical Research Laboratory
P.O. Box 620577
Fort Rucker, Alabama 36362-0577

8. PERFORMING ORGANIZATION REPORT NUMBER
USAARL 2010-17

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Material Command
504 Scott Street
Fort Detrick, Maryland 21702

10. SPONSOR/MONITOR'S ACRONYM(S)
USAMRMC

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This study evaluated the effects of 25 mg of intramuscular (IM) ketamine versus 10 mg of IM morphine on the performance of representative Warrior Skill Tasks in 48 healthy subjects. Ketamine demonstrated rapid onset of action and hemodynamic stability but did not result in improved Soldier performance. Overall, subjects reported more symptoms associated with ketamine versus morphine and placebo, chiefly among them dizziness, poor concentration, and feelings of happiness. Performance decrements on ketamine, when present, manifested as slower performance times rather than procedural errors. This may represent the adoption of a cautious posture suggested by risk propensity testing whereby the subject is aware of impairment trading speed for preservation of task accuracy. Despite the fact that subjects were more symptomatic on ketamine, the Warrior Skill Tasks were largely resistant to performance decrements suggesting that a trained task skill (autonomous phase) remains somewhat resilient to the drugged state at this dosage.

15. SUBJECT TERMS
ketamine, morphine, analgesia, pain control, Warrior Skill Tasks

16. SECURITY CLASSIFICATION OF: a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
UNCLAS	UNCLAS	UNCLAS	SAR	137	Loraine Parish St. Onge, PhD
					19b. TELEPHONE NUMBER *(Include area code)* 334-255-6906

Reset

Acknowledgements

The authors would like to express their sincere gratitude to the following people for their contributions to this project:

- Jim Chiaramonte, Edna Rath, Lana Milam, Mindy Vasbinder, Navdeep Saini, Adam Thompson, Arlene Breaux, and Stephanie Moon (study technicians) for their dedication and technical expertise.
- Brandy Dunn, PharmD (Clinical Pharmacist, Lyster Army Health Clinic) for her clinical pharmacy expertise and support.
- David Hataway (Emergency Medical Services, Lyster Army Health Clinic) for his contingency support in this endeavor.
- Julia Greene, RN (Chief Nurse, Aviation Medicine Clinic, Lyster Army Health Clinic) for her willing assistance and support.
- Elizabeth Stokes for assistance with all matters administrative.
- Diana Hemphill (Technical Information Officer), Sharon Fales (Librarian), and Loraine St. Onge, PhD (Technical Editor) of the USAARL Science Information Center for their invaluable assistance with literature reviews, manuscript editing, and publication requirements.

Table of contents

Table of contents (continued)

List of figures

Table of contents (continued)
List of figures (continued)

List of figures (continued)

List of figures (continued)

List of figures (continued)

List of tables

List of tables (continued)

List of tables (continued)

Introduction

Dosis sola facit veneum.

The Renaissance physician Paracelsus is often quoted as saying, "What is not poisonous? Everything is poisonous yet nothing is poisonous. The dose alone makes the poison." (Guggenheim, 1993). Certainly medicines and drugs can have quite varied results and clinical effects at different dosages. Furthermore, the intended therapeutic effect of a drug is not the sole consideration for the medical provider treating his patient—side effect profile, route and ease of administration, rate of absorption, bioavailability, body compartment distribution, metabolism, rate of elimination, therapeutic index, and toxicology are just a few of the factors that weigh on the decision of what drug to use and how much. Indeed, these are important points to mind when first considering why the military might be interested in the possibility of treating the pain of battlefield casualties with ketamine, a non-barbiturate dissociative anesthetic similar to phencyclidine.

Tragically, to varying degrees, casualties are inevitable in combat operations. Every field combatant Commander, medical unit Commander, and leaders at all levels incorporate casualty care and evacuation into operational planning. While lamentable in their own right, casualties can also jeopardize mission completion, reduce combat effectiveness, increase exposure and danger to other Soldiers, and drain precious resources. Tactical Combat Casualty Care (TCCC or TC3) is the military counterpart to the American College of Surgeons (ACS) Prehospital Trauma Life Support Course, a nationally recognized civilian program under the direction of the Committee on Trauma (ACS, 2010). The tenets of TCCC include Care under Fire, Tactical Field Care, and Tactical Evacuation Care with the focus on treating the casualty (saving preventable deaths), preventing additional casualties, and completing the mission (TCCC Curriculum, 2010).

As the situation dictates, sometimes the best initial medicine during care under fire is for the casualty to take cover, return fire, and "remain engaged as a combatant if appropriate" (TCCC, 2010). In other words, to the extent that the casualty can remain a capable, engaged Warfighter, he preserves fighting strength and unit capability—actions which may be essential to tactical fire superiority and enemy engagement. Ultimately this can serve to prevent additional casualties, preserve operational and tactical momentum, and further prosecute the mission. Even in later stages of care, a unit may still need the skills and capabilities of a casualty, as TCCC states, "Remember—effective hostile fire could resume at any time."

To state that analgesia is important in casualty care is a belittlement. The types of injuries encountered on the modern battlefield resulting from high-energy blast or direct fire weapons are horrific and cause tremendous pain. Since its discovery in 1805 and subsequent well-documented military use in the Crimean War and American Civil War, morphine (and its derivatives) has remained the mainstay for acute severe battlefield pain (Gaunt, Gill, & Aldington, 2009). Its perpetuation in this capacity speaks to its strengths and desirable qualities as a potent analgesic. Indeed, the 10 milligram (mg) intramuscular (IM) morphine injector is the current battlefield standard for acute severe pain. However, morphine can be associated with some untoward side effects (table 1), and the military medical community has searched for adjuvants and alternatives

to augment and/or spare morphine use in some instances (e.g., Connor, Ralph, & Aldington, 2009; Stamatos, Boedeker, and Crowl, 1995).

Table 1.
Side effects of morphine.

Sedation	Respiratory depression
Euphoria/dysphoria	Nausea and vomiting
Histamine release	Muscular rigidity
Cardiovascular depression	Smooth muscle spasm
Endocrine dysfunction	Tolerance and dependence
Constipation/ileus	Urinary retention

Based on this side effect profile, one can surmise that, depending on the dose, morphine might detract from a casualty's ability to "remain capable" on the battlefield. The Combat Medic Field Reference, for example, states that the casualty is considered non-ambulatory following administration of morphine (Bond, 2005). And TCCC mandates that combatants with altered mental status must be disarmed with the risk of using their weapons inappropriately (TCCC, 2010). Furthermore, the IM route is notoriously problematic in conditions of hemorrhage, hypovolemia, and hypothermia whereby absorption is poor, analgesia is unreliable, and overdose remains a concern with subsequent volume resuscitation during later stages of care.

So, while morphine is, indeed, a very good analgesic, one can see how the military might be interested in potential alternatives, adjuvants, and substitute routes of drug delivery for battlefield pain control. Indeed, the guidance of "improved drugs to manage pain" is listed specifically as a key technology to be explored and developed as a Health Service Support Force Operating Capability according to Training and Doctrine Command Pamphlet 525-66 (Department of the Army [DoA], 2008a). Likewise, pain control research remains a designated program area of the Army's Combat Casualty Care Research Program (CCCRP) with the mission of "fostering the development of biologics, pharmaceuticals, and medical devices that improve the first responder's capability to provide effective treatment more rapidly and as close to the place of the injury as possible." (CCCRP, 2010). Medics with direct combat experience, as well, have requested improved battlefield analgesia, in particular, seeking alternatives to morphine and alternate routes of administration (Maani, 2008).

In 2009, Smith, Russell, Mahoney, and Hodgetts at the Royal Centre for Defence Medicine (United Kingdom) conducted a study of clinical opinion assessing the effectiveness of current battlefield analgesia and options for improvement. Surveying 122 clinicians (emergency physicians and nurses, anesthesiologists, surgeons, intensivists, general practitioners, and combat medical technicians), more than half (52%) disagreed that IM morphine had the ideal analgesic properties for the military pre-hospital arena. The majority of respondents reported simplicity, reliability, and rapid onset of action of high importance. Furthermore, a majority (70%) responded that an analgesic more potent and with a more rapid onset than morphine was desirable, while 74% reported that a nasal spray was an acceptable delivery method.

The concept of exploiting routes of drug administration other than intramuscular (IM) is not new (e.g., Finn, Wright, Fong, Mackenzie, Wood, et al., 2004; Kotwal, O'Connor, Johnson, Mosely, Meyer, & Holcomb, 2004; Dale, Hjortkjaer, & Kharasch, 2002; Mycek, Harvey, & Champe, 1997). These may include buccal transmucosal, intranasal aerosol, transdermal, and others. Early intravenous (IV) access with more precise titration is ideal, but problematic in combat conditions (Smith, Russell, Mahoney, & Hodgetts, 2009; Kotwal et al., 2004).

Morphine is an excellent, time-tested battlefield analgesic for acute severe pain, but does have some shortcomings in certain instances (no drug is ideal, of course). And, the intramuscular delivery route can be problematic, especially with shock-states common with battlefield-type injuries. Certainly, the military medical community would be interested in exploring alternative drugs and routes of administration for combat casualty care. This study was sponsored by the Army's CCCRP in support of the Integrated Product Team (IPT) researching intranasal (IN) ketamine as a potential battlefield analgesic.

Background

Pain

The phenomenon of pain is complex entailing complicated interactions and pathways of peripheral nociceptors, a multitude of large and small myelinated and unmyelinated fibers, the dorsal root ganglion and dorsal column, the spinothalamic and spinoreticular tracts of the cord, and the limbic system and cerebral cortex (Stamatos, Boedeker, & Crowl, 1995). It includes ascending pathways, descending modulating pathways, and a host of neurotransmitters, vasoactive substances, and chemical mediators.

An individual's interpretation of painful stimuli still remains somewhat of a mystery even today and may be affected by personality, past experiences, emotional state, culture, and other factors (Paris & Yealy, 2002). Available pharmacological agents in the clinician's armamentarium are many including opioids, cyclooxygenase inhibitors, non-steroidal anti-inflammatory agents, alpha-2 receptor agonists, various antidepressants and antipsychotics, anticonvulsants, and others (Connor et al., 2009). Of these, the opioids are considered the mainstay for moderate to severe acute pain.

Morphine

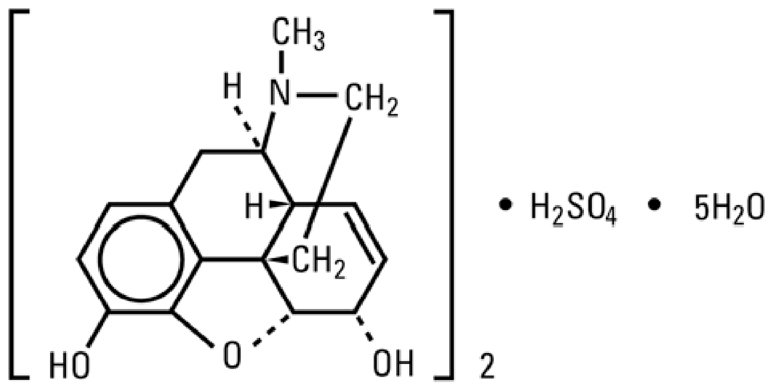


Figure 1. Morphine sulfate (Hospira, Inc., drug package insert, 2004).

The pharmacodynamic actions of opioids are primarily mediated through different opioid receptors in the spinal cord and brain including μ_1, μ_2, κ, and δ (Paris & Yealy, 2002). Morphine (figure 1), the major phenanthrene alkaloid of opium, is the opioid to which all other natural and synthetic opioids are compared (Stamatos et al., 1995). Morphine exerts its primary effects on the central nervous system (CNS) and organs with smooth muscle. For analgesia, μ receptors are widely distributed throughout the CNS with highest concentrations in the limbic system (hippocampus, amygdala, and frontal and temporal cortex), thalamus, hypothalamus, striatum, midbrain, and dorsal horn of the spinal cord (Hospira, 2004). Morphine is a Schedule II narcotic under the United States Controlled Substance Act (21 U.S.C. § 812). Specific receptor activity is listed in table 2.

Table 2.
Receptor activity of morphine.

Receptor	Major Effects
μ_1	Analgesia and pain modulation, respiratory depression, miosis, euphoria, depressed gastrointestinal activity, urinary retention
μ_2	Sedation, respiratory depression, nausea, mental clouding
κ	Analgesia, dieresis, sedation, dysphoria, mild respiratory depression, miosis
δ	Analgesia, dysphoria, delusions and hallucinations

Adapted from Couper & Logan (2004) and Paris & Yealy (2002).

Morphine has been used clinically for more than a hundred years, and the scientific literature is replete with information regarding mechanism of action, receptors, pharmacokinetics, pharmacodynamics, indications, side effects, and other information. Most clinicians are experienced with its use; a lengthy discourse on morphine is not indicated here, yet some points are worth brief remarks.

Morphine is amenable to many routes of administration: oral, intramuscular, intravenous, subcutaneous, rectal, epidural, and intrathecal. Glare and Walsh (1991) characterized the clinical pharmacokinetics of morphine as follows: peak plasma levels are achieved within 15-20 minutes for subcutaneous or intramuscular dosing, while oral peaks are achieved at approximately 30-90 minutes. Oral routes undergo significant first-pass hepatic metabolism, so peak levels following oral administration are much lower. Following absorption, morphine is readily and rapidly distributed (volume of distribution 1-6 Liters/kilogram) and crosses the blood-brain barrier. Plasma protein binding is approximately 20-35%.

Side effects of morphine were previously reported in table 1. Receptor activity is characterized in table 2. Couper and Logan (2004) provide a succinct summary of the performance effects of morphine as follows: "Laboratory studies have shown that morphine may cause sedation and significant psychomotor impairment for up to 4 hours following a single dose in normal individuals. Early effects may include slowed reaction time, depressed consciousness, sleepiness, and poor performance on divided attention and psychomotor tasks. Late effects may include inattentiveness, slowed reaction time, greater error rate in tests, poor concentration, distractibility, fatigue, and poor performance in psychomotor tests. Subjective feelings of sedation, sluggishness, fatigue, intoxication, and body sway have also been reported."

Ketamine

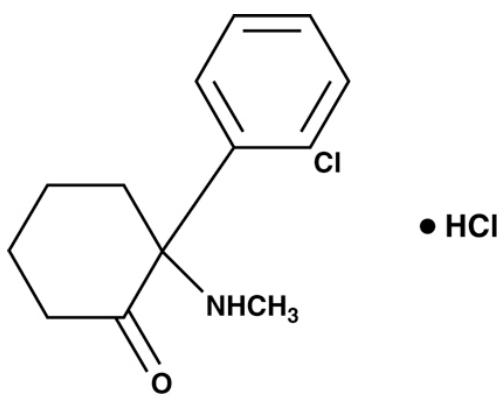


Figure 2. Ketamine hydrochloride (Hospira, Inc., drug package insert, 2005).

Ketamine (figure 2) is a non-opiate, non-barbiturate N-methyl-D-aspartate (NMDA) receptor antagonist first described in 1965 and approved for clinical use in 1970 (Aroni, Iacovidou, Dontas, Pourzitaki, & Xanthos, 2009). It was first evaluated in humans in 1966, and is the chloro-ketone analogue of phencyclidine (Jolly, Jain, & Sood, 2007). The drug is capable of producing a physiologic state known as "dissociative anesthesia" providing sedation, amnesia, and immobility whereby the patient appears awake but is unconscious and does not feel pain (Mycek et al., 1997). Ketamine non-competitively binds to the phencyclidine receptor inhibiting glutamate activation whereby the cortex sensory association areas, limbic system components, and thalamus are directly depressed. With input from the thalamus and brainstem, the limbic system processes sensory input along with information from the sensory cortex, so the CNS is

unable to receive or process sensory information (Aroni et al., 2009). In addition to the NMDA receptor, ketamine also exhibits analgesic effects via nitric oxide synthase inhibition, a neurotransmitter involved in pain perception (Aroni et al., 2009). Other purported receptor interactions include norepinephrine, serotonin, and muscarinic receptors (Hersack, 1994). Ketamine is a Schedule III drug under the United States Controlled Substance Act (21 U.S.C. § 812).

Although largely used as an anesthetic, interest in ketamine as an analgesic is not surprising given the NMDA receptor's significant role in pain perception. Furthermore, it has been known for over twenty-five years that ketamine interacts with opioid receptors (Finck & Ngai, 1982). Recommended analgesic dose ranges vary (0.4-1.0 mg/kg IM and 0.2-0.5 mg/kg IV) and are generally given as lower than that need for anesthetic purposes (5-10 mg/kg IM or 1-2.5 mg/kg IV) (Jolly et al., 2007; Wedmore, Johnson, Czarnik, & Hendrix, 2005). Schmid, Sandler, and Katz (1999) reviewed 28 studies examining the outcomes of low dose ketamine (defined as < 2 mg/kg IM or < 1 mg/kg IV) in the management of acute post-operative pain noting both IM and IV low dose ketamine provided effective analgesia. The authors noted ketamine as a potent and safe adjunct to systemic opioid analgesia and capable of a significant opioid sparing effect. Subramaniam, Subramaniam, and Steinbrook (2004), in a review of 37 trials utilizing ketamine as an adjunct to peri-operative opioid analgesia, noted the method of administration and the pain severity influenced the efficacy of the drug: ketamine worked best when used as a continuous IV infusion for operations with large opioid requirements although single bolus dosing for minor surgical procedures was also found to be safe and effective. Galinski, Dolveck, Combes, Limoges, Smail, et al. (2007) in a randomized double blind trial noted a considerable morphine sparing effect in trauma patients with initial severe acute pain who were given concurrent low dose intravenous infusion (IVI) ketamine (0.2 mg/kg) over 10 minutes.

A study into the bioavailability of ketamine and its metabolite norketamine indicates a strong hepatic first pass effect when ketamine is taken by GI routes (Yanagihara, Ohtani, Kariya, Uchino, Hiraishi, et al., 2003). The bioavailability of ketamine varies accordingly: 100% (IV); 45% (intranasal); 30% (per rectum); 30% (sublingual); 20% (oral). IM administration was not studied, but in other studies the bioavailability has been estimated at 93% (Clements, Nimmo, & Grant, 1982; Grant, Nimmo, & Clements, 1981).

The adverse effects of ketamine are generally grouped into cardio-respiratory effects, other systemic effects, psychotomimetic reactions (tending to induce hallucinations, delusions, or other symptoms of a psychosis), and performance deficits; most tend to be dose dependent. Krystal, Karper, Seibyl, Freeman, Delaney, et al. (1994) noted an increase in the blood pressure of healthy volunteers at dosage levels of 0.5 mg/kg IV over 40 minutes. Sedation and nausea tend to be no worse than with morphine alone (Bell, Dahl, Moore, & Kalso, 2005; Schmid, Sandler, & Katz, 1999; Galinski et al., 2007), or in some studies better (Kollender, Bickels, Stocki, Maruoani, Chazan, et al. 2008). However healthy volunteers (pain free) may experience higher rates of nausea and vomiting than that seen in the clinical setting (Krystal et al., 1994). Ghoneim, Hinrichs, Mewalt, and Peterson (1985) had 69% of healthy subjects experiencing nausea with 0.5 mg/kg IM ketamine.

Ghoneim et al. (1985) also reported frequent dizziness, floating sensations and perceptual

distortions; Lofwall, Griffiths, and Mintzer (2006) also found frequent altered balance in their study on healthy volunteers. With respect to psychotomimetic reactions, benzodiazepines are effective in reducing their incidence, but their concomitant use can present new or exacerbate other side effects. Schmid et al. (1999) reported psychotomimetic reactions as negligible at plasma levels < 50 ng/mL but with a dose related incidence beyond this level. In a Cochrane review, Bell et al. (2005) specifically stated that there were no psychotomimetic adverse effects in 21 of 37 trials. Lofwall et al. (2006) gave healthy volunteers bolus doses of ketamine whilst determining their cognitive performance and subjective experience in a double blind, placebo controlled crossover trial. Subjects on higher doses of ketamine (0.4 mg/kg IM) experienced significantly more perceptual distortions and dissociative effects than those on lower doses of ketamine (0.2 mg/kg IM). Krystal et al. (1994) reported similar findings at higher dosage levels with significant perceptual effects of all sensory modalities, paranoia and unusual thought content. Ketamine was anxiogenic at higher dosing but anxiolytic at lower dosing. Attention, vigilance, insight and recall were also affected at higher levels and subjects reported a significant sense of intoxication.

Annetta, Iemma, Garisto, Tafani, and Proietti (2005) provide a nice summary of the major neurologic, cardiovascular, and pulmonary effects of ketamine as outlined in table 3. In their review, the authors note that multiple prospective randomized studies have demonstrated the efficacy of low-dose ketamine for analgesia (especially as an adjunct to narcotics) with few adverse side effects.

Table 3.
Summary effects of ketamine.

System	Major Effects
Neurological	Dissociative anesthesia (cataleptic-like unresponsiveness), analgesia, emergence reactions, increased cerebral blood flow and intracranial pressure
Cardiovascular	Increased blood pressure, heart rate, and cardiac output, increased catecholamine levels
Pulmonary	Preserved upper airway reflexes and muscle tone, no significant ventilatory depression, bronchodilation and increased lung compliance, increased tracheobronchial secretions
Gastrointestinal	Increased salivary secretions, nausea and vomiting
Musculoskeletal	Increased skeletal muscle tone
Ocular	Increased intraocular pressure

Adapted from Aroni et al. (2009) and Annetta et al. (2005).

Couper and Logan (2004) provide a succinct summary of the performance effects of ketamine is as follows:

> Broad spectrum of cognitive impairments and marked dissociative effects. Increased distractibility and intensely visual or polysensual hallucinations. Impairment of immediate and delayed recall, and verbal declarative memory. Memory impairment is

associated with encoding or retrieval processes, and not accounted for by decreased attention. Impaired language function, failure to form and use memory traces of task relevant information. Overall decreased awareness, increased reaction time, distorted perceptions of space, non-responsiveness, and blurred vision.

Intranasal ketamine for casualty care

Department of Defense (DoD) involvement with the intranasal ketamine development effort began in approximately 2000. An analgesic product was envisioned that could provide acute pain relief while preserving the casualty's ability to perform Soldier tasks and retain functionality (Bell, 2009). Other desirable attributes included noninvasive delivery route, rapid onset and action, and opioid sparing effects. Javelin Pharmaceuticals, headquartered in Cambridge, Massachusetts, developed a proprietary nasal formulation of ketamine under the name Ereska™ for the management of acute moderate to severe pain (Javelin, 2010a).

Ereska™ is a 15% ketamine hydrochloride solution developed for intranasal delivery (approximately 40% bioavailability) intended for the treatment of acute moderate to severe pain under medical supervision. The product is intended as a single-use spray device (does not require synchronized inhalation) with one dose of 30 mg (12 mg/dose systemic absorption) delivered as one spray in each nare (Bell, 2009). Javelin Pharmaceuticals has recently completed a Phase III trial examining the efficacy of Ereska™ for use in post-operative orthopedic patients with a significant primary endpoint of Sum of Pain Intensity Differences over 0-6 hours (SPID-6) (Javelin, 2010b). Incidences of psychological side effects were reported as ≤ 3%, typically mild and transient (Javelin, 2009).

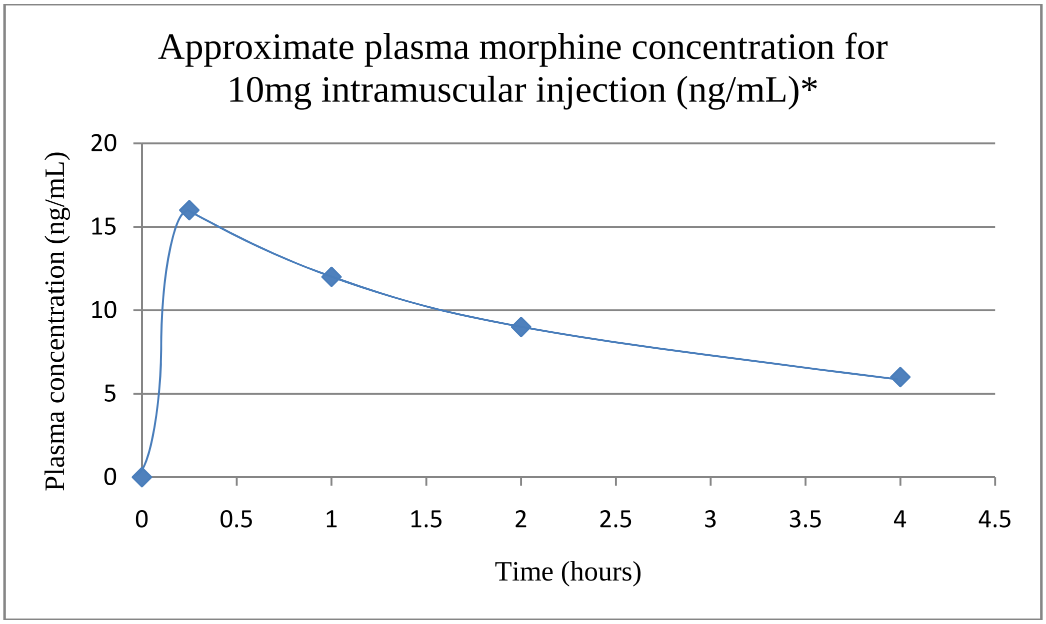
The Walter Reed Army Institute of Research (WRAIR) conducted preliminary testing in this effort evaluating cognitive performance effects of four dosages of ketamine (30, 60, 90, and 120 ng/mL) over 120 minutes of continuous IV infusion (Wesensten, n.d.). Cognitive tasks included the Psychomotor Vigilance Task (PVT), Grooved Pegboard Test (GPT), California Verbal Learning Task (CVLT), Wisconsin Card Sort Task (WCST), Tower of London (TOL), Wechsler Logical Memory Recall Test (WLMR), Balloon Analogue Risk Task (BART), Rapid Visual Information Processing (RVIP), Pattern Recognition Memory (PRM), Spacial Working Memory (SWM), Pennsylvania Emotion Differentiation Test (PEDT), Design Organization Task (DOT), Evaluation of Risks (EVAR), Biber Cognitive Estimation (BCE), and Clinician Administered Dissociative State Scale (CADSS). In summary, ketamine impaired response times to visual stimuli (PVT), impaired manual dexterity (GPT), impaired the ability to consolidate information (WLMR), impaired visual information processing accuracy (RVIP), impaired design organization accuracy (DOT), impaired cognitive estimation (BCE), and increased perseverative errors (WCST). Ketamine increased self-ratings of dissociation, but did not impair retrograde memory.

In an effort to more precisely delineate performance decrements in Soldier tasks, the U.S. Army Aeromedical Research Laboratory (USAARL) conducted the current study comparing the effects of the standard battlefield analgesic for acute severe pain, the 10 mg IM auto-injector, with an comparable ketamine dose representing the proposed IN product (60 mg, representing two doses of 30mg IN ketamine in the self-contained single-use spray device, at 40% IN

bioavailability equates to approximately to 25mg IM).

Test articles

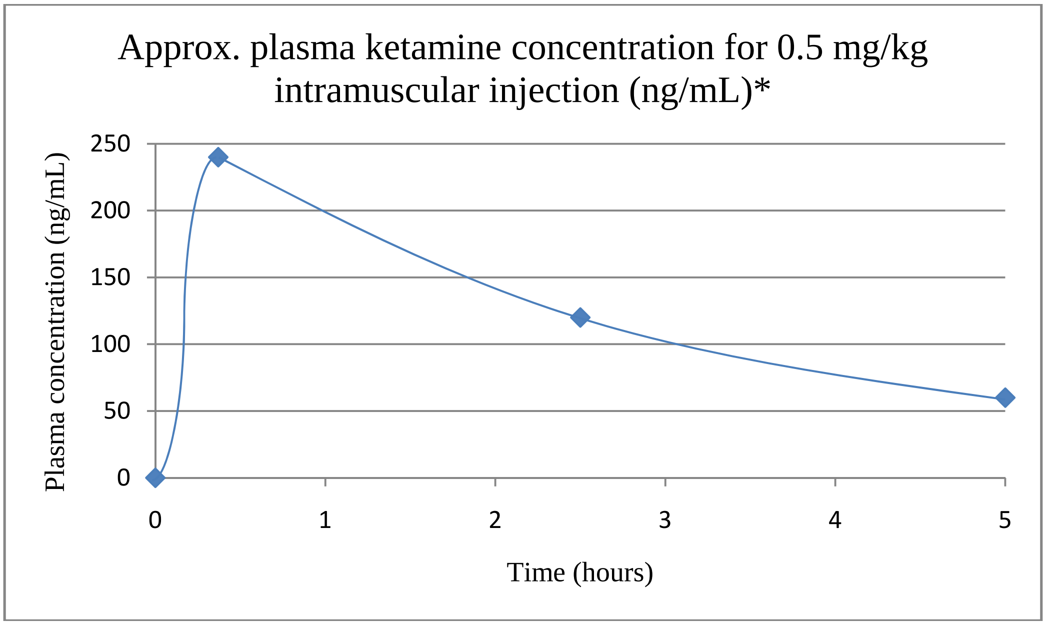
Raj, Sehgal, Hall, Sharma, Murrin, et al. (2004) characterized the plasma concentration of 10 mg of IM morphine for 19 subjects (87 kg ± 15) with a representative approximation is shown in figure 3. Note the first-order kinetics whereby the rate of drug metabolism is proportional to the concentration of free drug (e.g., a constant fraction of drug is eliminated per unit time).



Adapted from Raj et al. (2004).

Figure 3. Approximate plasma morphine concentrations following 10 mg IM.

Grant et al. (1981) and Clements et al. (1982) characterized the plasma concentration of 0.5 mg/kg of IM ketamine with a representative approximation shown in figure 4. Note that this is a larger dose than used in the current study, but the first-order kinetics is representative. Pharmacokinetics were variable in both reports with peak concentrations ranging from 100 to 425 ng/mL and time to peak from 5-30 minutes.



Adapted from Clements et al. (1982) and Grant et al. (1981).

Figure 4. Approximate plasma ketamine concentrations following 0.5 mg/kg IM.

The current study compared the performance decrements of 10 mg of IM morphine (representing the standard 10 mg morphine auto-injector used by combat medics) with 25 mg of IM ketamine (representing the bioequivalence of two doses of 30 mg IN ketamine) with saline placebo. A description of morphine and ketamine were given previously. Pharmacokinetics of the test articles are listed in table 4.

Note that both drugs share some similar characteristics, but ketamine has a faster time to peak effect. Morphine does cross the blood-brain barrier (BBB), but with difficulty due to poor lipid solubility, high protein binding (30-35%), and rapid conjugation and ionization. Ketamine has faster onset (effect) due to high lipid solubility, low protein binding (12%), and is metabolized by CYP450 enzymes (Dunn, 2010). Following this rapid onset, the anesthetic effect is terminated by a combination of redistribution (half-life 11 minutes) from the CNS to slower equilibrating tissues and hepatic transformation, not metabolism (Dunn, 2010; Hersack, 1994).

Table 4.
Pharmacokinetics of study medications.

	Time to Peak Effect (min)	Time to Peak Concentration (min)	$T_{1/2}$* (hours)	Elimination Kinetics
IM‡ Ketamine	3-15	15-30	2-3	First-order§
IM‡ Morphine	15-30	10-60	2-4	First-order§

Adapted from Dunn (2010) and Micromedex (2010).
*$T_{1/2}$ = drug half-life
‡IM = intramuscular route of delivery
§First-order kinetics = rate of drug metabolism is proportional to the concentration of free drug (e.g., a constant fraction of drug is eliminated per unit time). Note: after four half-lives, elimination is 94% complete for first-order kinetics.

Study objectives and hypothesis

The overall objective of this study was to evaluate the effects of ketamine on representative military tasks compared to the currently fielded analgesic agent, morphine. Direct comparisons included 25 mg IM ketamine versus10 mg of IM morphine versus saline placebo. Performances within the individual tasks were measured using time and task accuracy data collection.

Objective 1. Compare and quantify the performance effect of ketamine, morphine and placebo on representative military tasks using a test battery of military training standards and measures of performance.

Objective 2. Identify and report any adverse events related to the administration of analgesic levels of ketamine in a simulated training environment.

Hypothesis. 25 mg of IM ketamine will produce fewer and less severe performance decrements on the representational military tasks in the test battery than 10 mg IM morphine.

Methods

Study overview

The study consisted of a blinded, placebo controlled triple cross-over design including three arms, ketamine versus morphine versus placebo:

- 25 mg of ketamine (50 mg/mL); 0.5 mL IM (deltoid)
- 10 mg of morphine (25 mg/mL); 0.4 mL IM dosing (deltoid)
- 0.9% sodium chloride (saline) solution; 0.5 mL IM dosing (deltoid)

There were no induced pain stimuli to subjects. Testing consisted of representative military tasks based on the Soldier’s Manual of Common Tasks (Warrior Skills). Data collection was

completed over a 6-month duration.

Subject testing was completed over 7-day blocks. Within each week-long block, a maximum of three groups of four subjects were scheduled (maximum 12 per week). Subjects presented with varying military backgrounds and experience levels with the Warrior Skills, so day 1 (Saturday) was comprised of familiarization with the performance tasks and testing procedures followed by training to asymptote. Day 2 (Sunday) entailed baseline testing only. Testing under the three (drugged) study conditions was completed Monday, Wednesday, and Friday. Subjects remained on-site for no fewer than 8 hours after dosing for continued monitoring and adequate drug washout prior to release. The interim Tuesday and Thursday were reserved for drug wash-out and rest. A representative study timetable is depicted in table 5.

Table 5.
Illustrative study timetable for seven-day data collection period.

	SAT	**SUN**	**MON**	**TUE**	**WED**	**THU**	**FRI**
	In-process (Starts 0700)	**Baseline**	**Drug Condition 1**	**Day Off**	**Drug Condition 2**	**Day Off**	**Drug Condition 3**
0745	Task Block Practice (subjects staggered throughout day) Subjects released when competent in all tasks	Task Block Baseline Test Subjects 1 - 4	**Dosing** Subjects 1 – 4 Task Block Tests		**Dosing** Subjects 1 – 4 Task Block Tests		**Dosing** Subjects 1 – 4 Task Block Tests
0900		Task Block Baseline Test Subjects 5 – 8 Subjects 1 - 4 released	**Dosing** Subjects 5 – 8 Task Block Tests		**Dosing** Subjects 5 – 8 Task Block Tests		**Dosing** Subjects 5 – 8 Task Block Tests
1015		Task Block Baseline Test Subjects 9 – 12 Subjects 5 – 8 released	**Dosing** Subjects 9 – 12 Task Block Tests		**Dosing** Subjects 9 – 12 Task Block Tests		**Dosing** Subjects 9 – 12 Task Block Tests
1145		Subjects 9 – 12 released					
1200			Lunch		Lunch		Lunch
1600			Subjects 1 – 4 released		Subjects 1 – 4 released		Subjects 1 – 4 released
1715			Subjects 5 – 9 released		Subjects 5 – 9 released		Subjects 5 – 9 released
1830			Subjects 9 – 12 released		Subjects 9 – 12 released		Subjects 9 – 12 released

The order of drug administration was initiated with a roll of a six-sided dice, then completed in a pseudo-randomized fashion ensuring even subject numbers per drug group (eight subjects in each of six drug groups) (table 6). Drug order and dose administration to subjects was blinded to both subject and study investigators throughout (study physicians remained unblinded to the drug conditions for safety).

Table 6.
Test article (drug) group orders.

	Order of Drug Administration					
	Drug Order 1	**Drug Order 2**	**Drug Order 3**	**Drug Order 4**	**Drug Order 5**	**Drug Order 6**
Dose 1 (Mon)	Morphine	Morphine	Ketamine	Ketamine	Placebo	Placebo
Dose 2 (Wed)	Ketamine	Placebo	Morphine	Placebo	Morphine	Ketamine
Dose 3 (Fri)	Placebo	Ketamine	Placebo	Morphine	Ketamine	Morphine

While subjects performed tasks and were tested individually, they were dosed in groups of four (or less during weeks with fewer subjects). This co-treatment of each group (i.e., all ketamine, all morphine, or all placebo) helped to ensure blinding (since it may be obvious if some members of the group were drugged and others were not). Colored t-shirts were assigned to the three groups using a simple stop-light pattern: group one wore red, group two wore yellow, and group three wore green. In this manner, whenever subjects were assembled together (e.g., post-testing convalescent period), they were readily identifiable by group to the technicians. This facilitated the data collection (e.g., timing of vital signs) and served to increase safety (e.g., if a subject had a medical problem, the study physician immediately knew what drug the subject had received). Shirts were configured with subject's number on the sleeve and chest.

Study population

Recruitment, consent, and screening

Volunteer subjects were recruited from a pool of healthy male and female adult Soldiers at the Army Aviation Center of Excellence, Fort Rucker, Alabama. Volunteers included active duty enlisted Soldiers, Warrant Officers, and Officers. Interested individuals attended a mandatory informational briefing. These briefings were conducted by the principal or associate investigator, and subjects were free to ask any questions. This was followed by informed consent. The informed consent process was quite comprehensive detailing voluntary nature of participation, eligibility and inclusion/exclusion criteria, study procedures, overview of tasks and testing schedule, risks and discomforts, potential benefits, protections, precautions and safeguards, follow-up, withdraw and termination, compensation, medical care, questions, and confidentiality. Unlimited time was allowed all potential subjects to complete this process. An ombudsman was present for all informed consents. An external medical monitor was assigned to the study.

Inclusion criteria

Healthy male and female Soldiers between the ages of 19-44 years were included (19 is the age of majority in Alabama). Volunteers had two options for participation. Volunteers were required to be on leave status with a leave form (DoA Form 31) signed by their Command (option A, subject reimbursed $500). Or, volunteers had the option to not take leave, but were required to have a memorandum from their Command specifying USAARL as their place of duty during the testing week (option B, no compensation to subject).

Exclusion criteria

Exclusion criteria were established for subject safety and to prevent potential confounding factors. Once enrolled in the study (defined by attendance at the study information briefing and completion of the informed consent), subjects completed medical screening forms and met individually with one of the study physicians to determine inclusion. Medical exclusion criteria are outlined in appendix A. In addition to the initial screening, subjects again received a brief medical screening with a study physician on each of the three mornings (Monday, Wednesday, and Friday) prior to dosing to assess any changes in health, acute illness, any new medications (including over-the-counter), alcohol consumption, etc.

Morphine and ketamine are teratogenic, and listed as Pregnancy Category C and D, respectively. Female subjects volunteering for the study submitted urine specimens for pregnancy testing at the nearby Lyster Army Health Clinic (LAHC) at the time of initial enrollment medical screening and on each of the three mornings prior to dosing. Specimens were certified negative by the study physician. Subjects were also excluded for caffeine intake > 500 mg/day, alcohol consumption > 6 drinks/week, and nicotine use on a regular basis within three months of enrollment. Subjects were restricted from alcohol and nicotine during the study, and required to maintain caffeine consumption < 500 mg/day.

Description of test activity

Test metrics

Testing was designed to evaluate performance on representative military tasks based on the Soldier's Manual of Common Tasks—essential warrior skills that Soldiers must be able to perform in an operational environment (DoA, 2008b, 2006). These tasks form the baseline of military competence in the field; and with that, they provide an opportunity to assess Soldier vigilance, critical thinking, judgment and skilled performance within a military context. The tasks included are outlined in table 7.

Table 7.
Soldier tasks used for test metrics.

Assessment	Comment*
Engage Targets with an M16 or M4 Series Rifle‡	Warrior Skill Task No. 071-311-2007 (M16) or 071-100-0003 (M4)
Correct Malfunctions of an M16 or M4 Series Rifle	Warrior Skill Task No. 071-311-2029 (M16) or 071-100-0008 (M4)
Shoot—Don't Shoot (Identify Friend or Foe[IFF]) ‡	See note.
Protect Yourself from Chemical, Biological, Radiological, and Nuclear (CBRN) Injury or Contamination with Mission-Oriented Protective Posture (MOPP) Gear	Warrior Skill Task No. 031-503-1015
Protect Yourself from Chemical and Biological (CB) Contamination Using Your Assigned Protective Mask	Warrior Skill Task No. 031-503-1035
Perform Voice Communications	Warrior Skill Task No. 113-571-1022
Request Medical Evacuation	Warrior Skill Task No. 081-831-0101
Evaluation of Risks (EVAR) Visual Analogue Scale	Self-administered questionnaire
Symptom questionnaire	Technician administered questionnaire
Vital Signs	Technician administered

*Warrior Skill Tasks were extracted from the Soldier's Manual of Common Tasks, Warrior Skills Level 1 (Soldier Training Publication No. 21-1-SMCT) (DoA, 2006) and Soldier's Manual of Common Tasks, Warrior Leader Skills Level 2, 3, and 4 (Soldier Training Publication No. 21-24-SMCT) (DoA, 2008b).
‡Shooting tasks were conducted utilizing a computerized simulation range using the Engagement Skills Trainer 2000 (EST 2000). See paragraph below for more detail.
Note: Shoot—Don't Shoot IFF scenario was conducted using the M9 pistol. Warrior Skill Task No. 071-004-0006 corresponds to Engage Targets with an M9 Pistol.

All data collection and subject monitoring were completed at USAARL. Shooting and related weapon tasks were completed on the EST 2000 simulated range. Other tasks were completed at stations outfitted with the necessary tactical equipment and scenarios. Testing areas were padded for subjection projection. All tasks were video recorded for safety, reference, and to support subsequent data analysis in the event of loss of data or the need to verify findings (figure 5).

Figure 5. Technician in far corner observing video feed of subjects.

<u>EST 2000</u>

The EST 2000 is the U.S. Army's small arms training device, and includes part of the Army Infantry School's Basic Rifle Marksmanship (BRM) strategy. The EST 2000 is fielded to all U.S. Army components and facilitates marksmanship training, static unit collective gunnery and tactical training, as well as judgmental use of force training. The EST 2000 consists of an instructor-operator station (seen in the foreground in figure 5), a high-resolution projector, a detection system, an air compressor, a screen, cabling and hoses to connect to lane position weapon boxes, and the associated small arms weapons (figures 6 and 7). The USAARL EST 2000 includes five firing position lanes. The weapons are slightly modified to interface with the system but still maintain their form, fit, feel, and function.

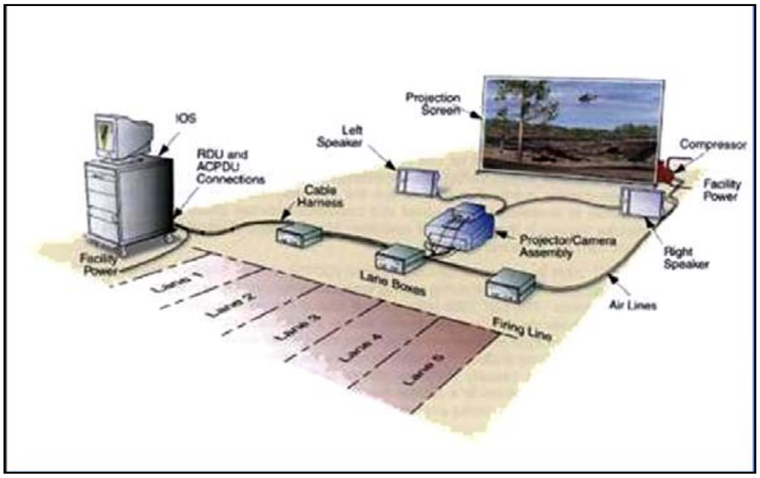


Figure 6. EST 2000 set-up (Anthony, 2006).

Figure 7. Soldier firing on EST 2000. Note: face intentionally blurred.

The USAARL EST 2000 possesses the capability to not only record the number of hits and misses, but also to determine shot radius (accuracy in the form of distance of the shot from center of mass [CM] of the target), reaction time (latency of trigger pull from the time of target presentation), and root mean square (RMS) distance from target CM as a measure of aiming drift (figure 8).

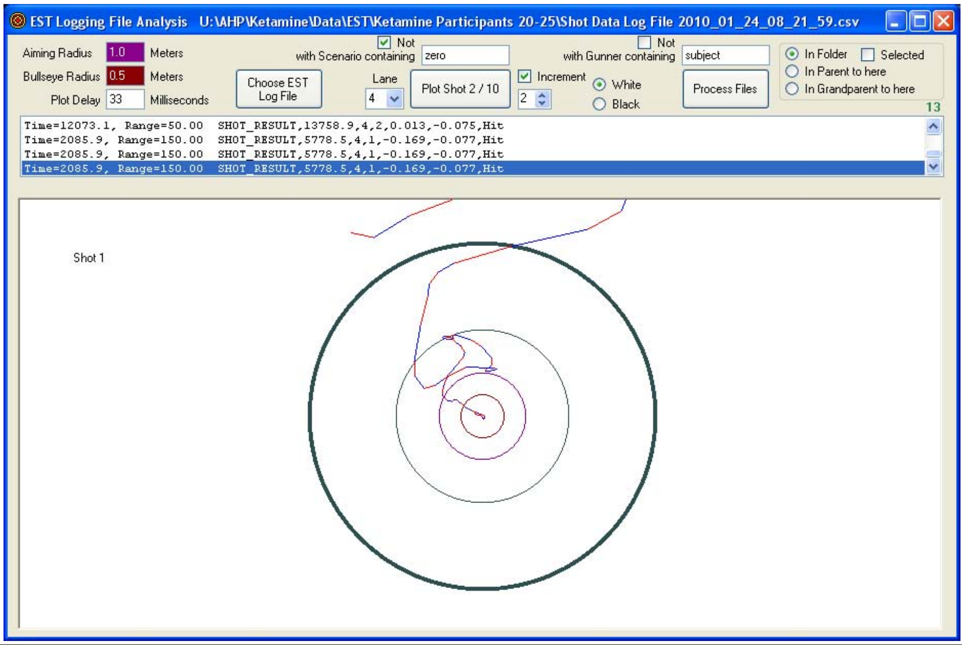


Figure 8. Computer screen shot depicting aiming trace to determine root mean square.

<u>Engage targets with an M16 or M4 series rifle</u>

This assessment is a basic rifle marksmanship task involving either the M16 or M4 long rifle engaging silhouette targets on the EST 2000 (figures 9 and 10). A weapon zero was accomplished during training session on day one (Saturday). The standard M16 or M4 Record Fire scenario runs for approximately 4 minutes and consists of 40 timed targets at ranges from 50-300 meters with 40 rounds of ammunition. The scenario entails the subject firing from three positions: prone supported, prone unsupported, and kneeling. Dependent measures included number of hits, reaction time to trigger pull, shot radius from CM of the target, and RMS of the aim trace.

Figure 9. Soldier engaging targets with M4 rifle. Note: face intentionally blurred.

Figure 10. EST 2000 screen depicting targets for engagement with rifle.

Correct malfunctions of an M16 or M4 series rifle

The immediate action for a rifle malfunction is governed by the SPORTS acronym, standing for slap upward on the magazine to ensure its seated, pull the charging handle back, observe the ejection of the cartridge and check for obstructions, release the charging handle to feed another round into the chamber, tap the forward assist, and squeeze the trigger. The weapon stoppage was simulated on a modified EST 2000 weapon immediately following the record fire task of engaging targets. Dependent measures included task accuracy and time to task completion.

Shoot—Don't Shoot (Identify Targets)

In this task, targets are presented one at a time at a distance of 20 meters for 2 seconds duration in a pseudo-random fashion with an inter-target delay interval of 2 seconds. This was designed specifically for the subject to rapidly perceive and correctly identify the target (friend, enemy, or neutral) and subsequently engage appropriately (or restrain) with the M9 pistol. Targets consisted of 15 friendly targets, 15 enemy targets and 15 neutral targets (figure 11). Dependent measures included number of hits, reaction time to trigger pull, shot radius from CM of the target, and RMS of the aim trace.

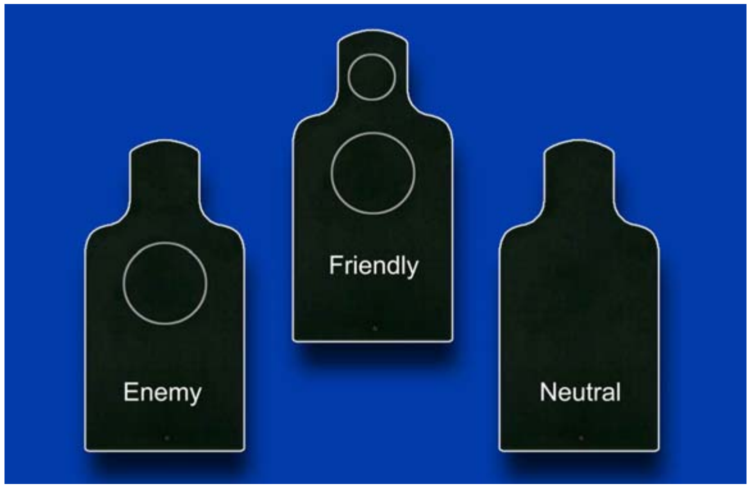


Figure 11. Identify targets.

Mission-Oriented Protective Posture (MOPP) gear and protective mask

Subjects were tested on donning their protective mask and Mission Orientated Protective Posture (MOPP) gear corresponding to the Warrior Skill Tasks of protecting self from CB contamination using protective mask (figure 12), and protecting self from CBRN contamination (with complete MOPP gear ensemble).

Figure 12. Soldier tested on donning protective mask.
Note: eyes intentionally blurred.

Protection of self from CB contamination using the mask was divided into two tasks. The first entailed donning, clearing, and checking the mask (must be completed within 9 seconds). The second entailed securing the hood. The Soldier's Manual of Common Tasks imposes no

time requirements on the second task to pass (only that it is completed properly), but time was recorded for purposes of this study. Dependent measures included number of errors and time to completion.

Protection of self from CBRN contamination was divided into four tasks in accordance with the Soldier's Manual of Common Tasks whereby the task numbers correspond with the MOPP level (1 = don trousers and jacket; 2 = don overboots, 3 = don protective mask, and 4 = don protective gloves). The Soldier skill requires all tasks to be completed within eight minutes or less, and each task was also timed for purposes of this study. Dependent measures included task accuracy and time to task completion.

Perform voice communications and request medical evacuation

In this task, subjects were presented with disassembled parts of an AN/PRC-90 handheld radio. Subjects were tested on speed and accuracy of bringing the radio to mechanical functionality and entering the radio net using correct call signs, sequence, prowords, and phonetic alphabet and numerals. After entering the net, subjects were required to interpret a multiple casualty scenario, extract pertinent information, and transmit a standard 9-line medical evacuation (MEDEVAC) request providing all necessary information and using proper brevity codes (figure 13). The 9-line MEDEVAC was separated into two tasks: task 1 consisted of MEDEVAC lines 1-5 (must be completed within first 25 seconds of radio transmission), and task 2 consisted of lines 6-9 (no time limit for completion). Dependent measures included task accuracy and time to task completion.

Figure 13. Soldier transmitting MEDEVAC request via radio.

Evaluation of Risks (EVAR) visual analogue scale

Impaired judgment can manifest in situations where an individual engages in behavior where the risks far outweigh the probable advantages. The propensity to engage in or avoid such risky behavior and situations was assessed using the Evaluation of Risks Questionnaire, which was originally developed and validated by Sicard, Jouve, and Blin (2001) and used in previous research with Special Operations Forces. Killgore, Vo, Castro, and Hoge (2006) established the reliability and validity of an English version of the EVAR which consists of 24 overlapping items distributed among three factors (the original French version is distributed among five factors): *risk/thrill-seeking, need-for-control,* and *self-confidence*.

In this study, the response format of the scale was modified from individuals marking a point along a 100-mm bipolar visual analogue scale to marking evenly distributed “bubbles” along the visual analogue scale. The test was administered at baseline and then midway between completion of Warrior Skill Tasks for each dose day.

Symptom questionnaire

The subjective symptom questionnaire developed for this study consisted of 20 possible side effects (table 8) with an option to record any additional symptoms verbatim if not included among the given list. Subjective severity, assessed at the time of completion, was categorized as mild, moderate, or severe. The questionnaire was administered by technicians pre intervention, and at intervals of 10 minutes, 40 minutes, 70 minutes, 4 hours, and 8 hours post intervention.

Table 8.
Symptom checklist.

Nervousness	Feelings of excitement	Jitteriness
Feelings of aggression	Feelings of happiness/elation	Tiredness
Dizziness	Racing heartbeat	Pounding heart or heartbeat
Headache	Nausea	Vomiting
Tremor	Double vision	Blurred vision
Itching	Disordered thought process	Poor concentration
Unreal thoughts	Any noticeable drug effect	Other

Vital signs

Pulse, blood pressure, respiratory rate, oral temperature, and room air pulse-oximetry were measured on all subjects by a study technician pre-intervention (baseline), and at time sessions of 10 minutes, 40 minutes, 70 minutes, 4 hours, and 8 hours post-intervention (figure 14). All medical equipment was verified to be within its calibration standards prior to commencement of data collection (and remain so for duration of study) by the laboratory’s medical maintenance section.

Figure 14. Vital signs monitoring. Note: face and vital signs intentionally blurred.

Subject safety

Medial exclusion criteria were established for subject safety and served to minimize the possibility of serious medical events. The study physicians (only) remained unblinded to study medications for safety purposes. All technicians and study personnel were trained and verified current on Basic Life Support (BLS) and received a class from the study physician regarding the test articles. Simulated emergency medical scenarios were run at the direction of the study physician with mock subjects during the preparatory phases of the study. Specific medical stop criteria and immediate study physician notification criteria were established in the protocol for all technicians.

Subjects remained under constant supervision by study personnel (to include the latrine) during data collection, and were monitored on a minimum of one-to-one basis during acute drug effect. Specific symptom inquiries and vital signs were assessed regularly during data collection per protocol. At least one study physician was on-site at all times. No subject was released from the study at the conclusion of testing until cleared by the study physician.

Emergency equipment immediately available included oxygen, airway equipment, and an Automatic External Defibrillator (AED). This equipment was checked every morning prior to data collection. On-site rescue medications included opioid antagonists, benzodiazepines (psychomimetic reactions), and an EpiPen® auto-injector (anaphylaxis). Emergency Medical Services (EMS) with Advanced Cardiac Life Support (ACLS) remained on site and under the direction of the study physician during acute drug effect (and available via activation at other

times). Non-emergent side-effects (e.g., nausea and vomiting), when warranting medical intervention or for subject comfort, were managed at the Lyster Army Health Clinic (across the street from data collection site) by one of the study physicians. Subjects on flight status received a 3-week temporary medical suspension (DA Form 4186) specifying “duties not including flying” for a three week period following completion of their enrollment.

Results

Subject demographics

Sixty-four Soldiers enrolled in the study (as defined by sitting for the introductory briefing and completing the informed consent process). Nine subjects did not meet the inclusion criteria based on subsequent medical screening with study physicians. Fifty-five subjects met inclusion criteria. Six subjects elected not to participate (mostly due to scheduling conflicts). Forty-nine subjects presented for data collection. One subject completed baseline testing but was not dosed due to a medical condition developing after baseline testing. Forty-eight subjects participated in data collection and completed the study. A summary table of significant results is outlined in appendix C.

Of the 48 participating subjects, one subject did not receive one of the three drug conditions due to a contraindication discovered at that morning’s medical screening. Therefore, the maximum sample size for some data analysis was 47. All 49 subjects presenting for data collection received post-study follow-up with the study physicians. There was one subject withdrawn and no losses to follow-up. Study totals are listed in table 9.

Table 9.
Study subject totals.

	No. Subjects
Total Enrolled	64
Number screened—did not meet inclusion criteria	9
Number screened—met inclusion criteria	55 (6 elected nonparticipation)
Number participated in study	49
Number completed study	48 (1 subject missed one dose for medical reasons.)
Number completing follow-up	49
Number withdrawn	1 (Subject was not dosed for medical reasons.)
Number lost to follow-up	0

Data were collected on 48 subjects; three subjects were female. Ages ranged from 22-42 years. Subject Body Mass Index (BMI) ranged from 22.5-32.5 kg/m^2. Soldier ranks ranged from sergeant (E-5) to Captain (O-3). Eight Military Occupational Specialties (MOS) were represented. Subject ages, BMI, ranks, and MOS's are depicted in figures 15, 16, 17, and 18, respectively.

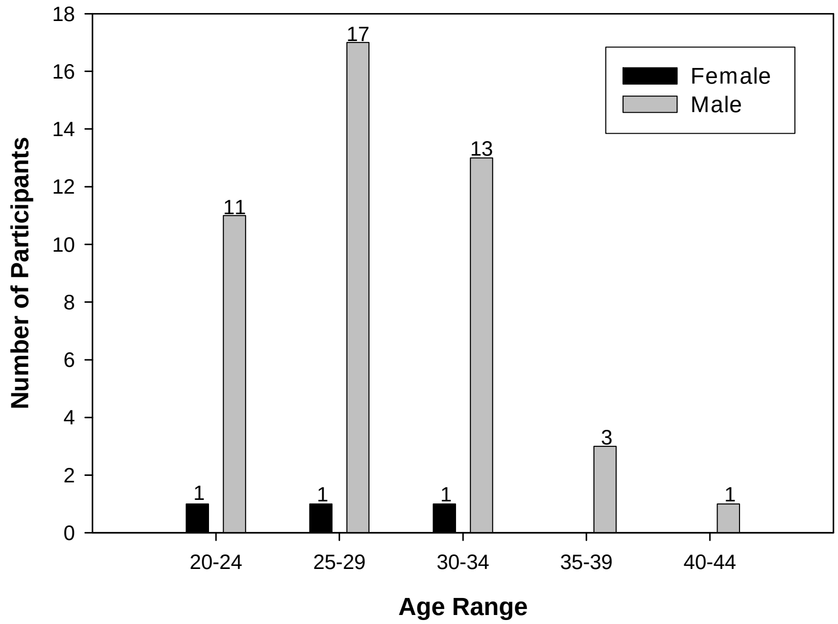


Figure 15. Subject ages and gender.

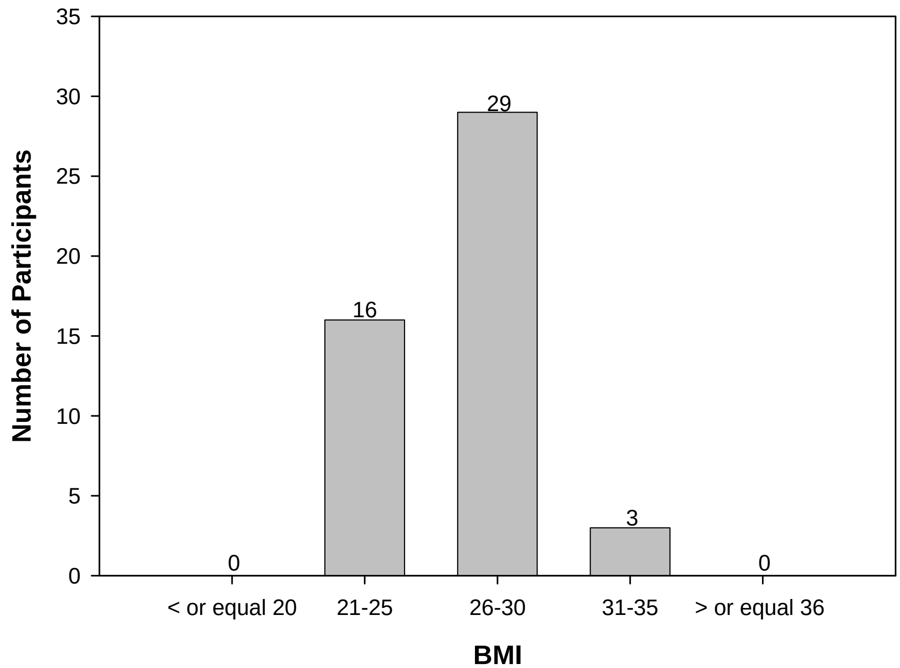


Figure 16. Body Mass Index of subjects.

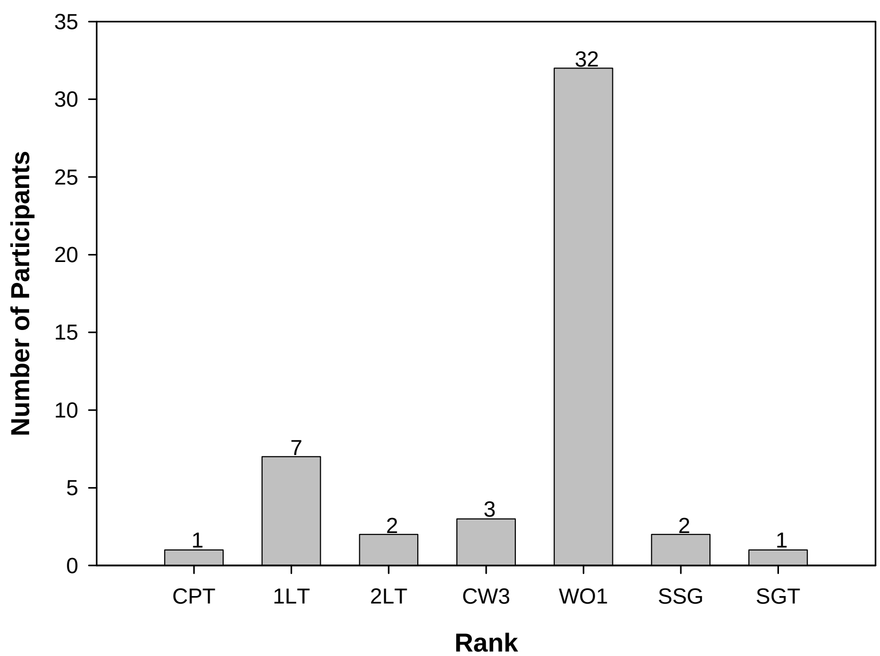


Figure 17. Soldier ranks of subjects. (Note: CPT-Captain, 1LT-First Lieutenant, 2LT-Second Lieutenant, CW3-Chief Warrant Officer 3, WO1-Warrant Officer 1, SSG-Staff Sergeant, SGT-Sergeant)

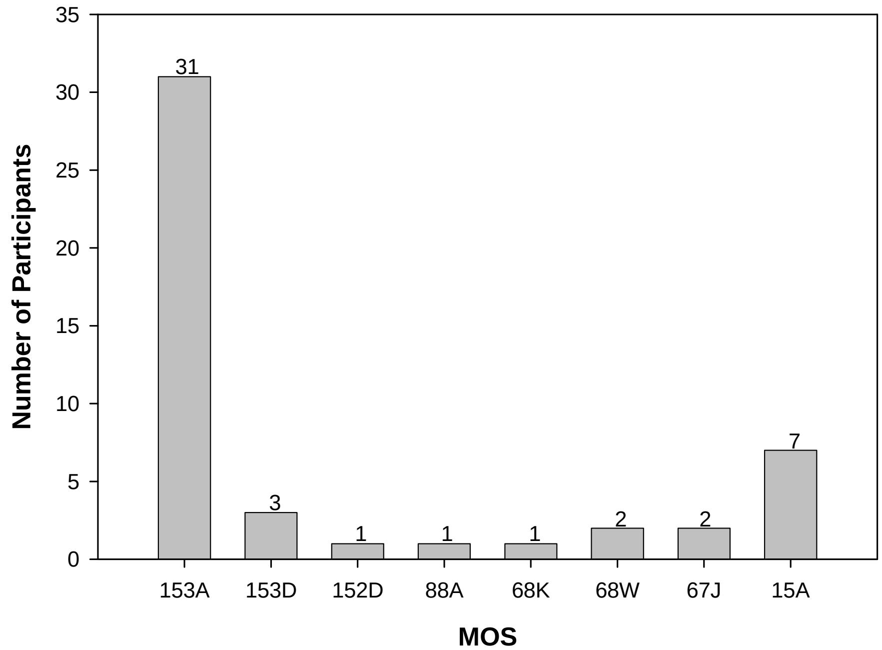


Figure 18. Subjects by Military Occupational Specialty. (Note: 153A-Rotary-wing Warrant Officer Aviator, nonspecific; 153D-Warrant Officer Aviator, UH-60; 152D-Warrant Officer Aviator, OH-58D; 88A-Transportation Officer, General; 68K-Enlisted Medical Laboratory Specialist; 68W-Enlisted Healthcare Specialist; 67J-Aeromedical Evacuation Officer; 15A-Aviation Officer, General)

Vital signs

Vital sign measurements were comprised of six dependent measures: systolic and diastolic blood pressure, pulse, oral temperature, respiration rate, and oxygen saturation. The data were analyzed using 5 (session) x 3 (drug) x 3 (report time) mixed model ANOVAs. The variable *session* was a within-subjects factor and its five levels were at +10 minute, +40 minute, +70 minute, +4 hour, and +8 hour drug administration. The variable *drug condition* was also a within-subjects factor and its three levels were ketamine, morphine, and placebo. The between subject factor was *report time*, and its three levels were 0745, 0900, and 1015 corresponding to the times of the drug doses. The scores were baseline corrected. Respiration rate data were unavailable for two subjects (n = 45). The remaining analyses were conducted with data from 47 subjects.

Systolic blood pressure

There was a significant main effect of session, F (2.776, 122.129) = 15.412, p < .001 (Greenhouse-Geisser corrected), observed power = 1.00. Pairwise comparisons revealed that subjects' mean systolic blood pressure was significantly greater during the +10 minute drug

administration period than the other four sessions. There was also a significant main effect of drug condition, F (1.642, 72.229) = 11.981, $p < .001$ (Greenhouse-Geisser corrected), observed power = .985. Pairwise comparisons revealed that overall, subjects' mean systolic blood pressure was greater for the ketamine condition than the morphine ($p = .013$) and placebo ($p < .001$) conditions. The main effect of report time was not significant, F (2, 44) =1.785, $p = .180$, observed power = .354.

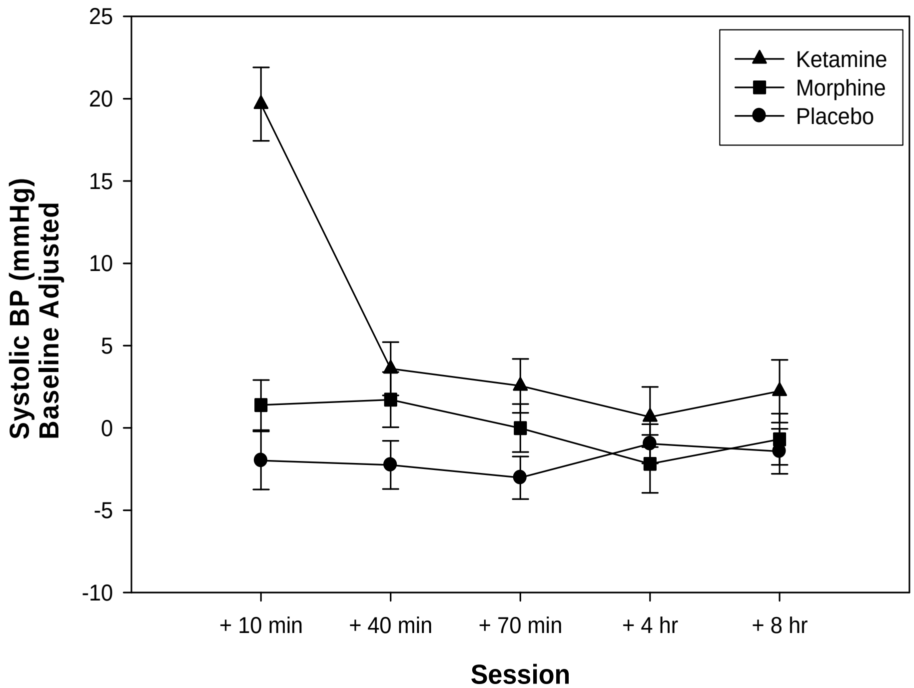


Figure 19. Systolic blood pressure by drug and time session.

There was also a significant interaction between drug condition and session, F (8, 352) =17.465, $p < .001$, observed power = 1.00. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($\alpha = .05/15 = .003$). Results for the t-tests are presented in table 10. As shown in figure 19, during the +10 minute drug administration period, subjects' mean systolic blood pressure in the ketamine condition was significantly higher than for the morphine and placebo conditions. In addition, subjects' mean systolic blood pressure for the ketamine condition was significantly higher than placebo for the +40 minute drug administration period.

Table 10.
Post hoc results for systolic blood pressure.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.025
+40 minutes	ketamine vs. morphine	.319
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.004
+70 minutes	ketamine vs. morphine	.293
	ketamine vs. placebo	.011
	morphine vs. placebo	.037
+4 hours	ketamine vs. morphine	.198
	ketamine vs. placebo	.729
	morphine vs. placebo	.140
+8 hours	ketamine vs. morphine	.306
	ketamine vs. placebo	.265
	morphine vs. placebo	.988

* significant (Bonferroni correction)

Diastolic blood pressure

There was a significant main effect of session, F (2.683, 118.039) = 12.732, $p < .001$ (Greenhouse-Geisser corrected), observed power = .999. Pairwise comparisons revealed subjects' mean diastolic blood pressure during the +10 minute and +40 minute drug administration period were significantly higher than the +70 minute, +4 hour, and +8 hour periods. There was also a significant main effect of drug condition, F (2, 88) = 7.409, $p = .001$, observed power = .933. Pairwise comparisons revealed that overall, subjects' mean diastolic blood pressure was significantly greater for the ketamine condition than the placebo ($p = .003$) condition. The main effect of report time was not significant, F (2, 44) = 1.207, $p = .309$, observed power = .250.

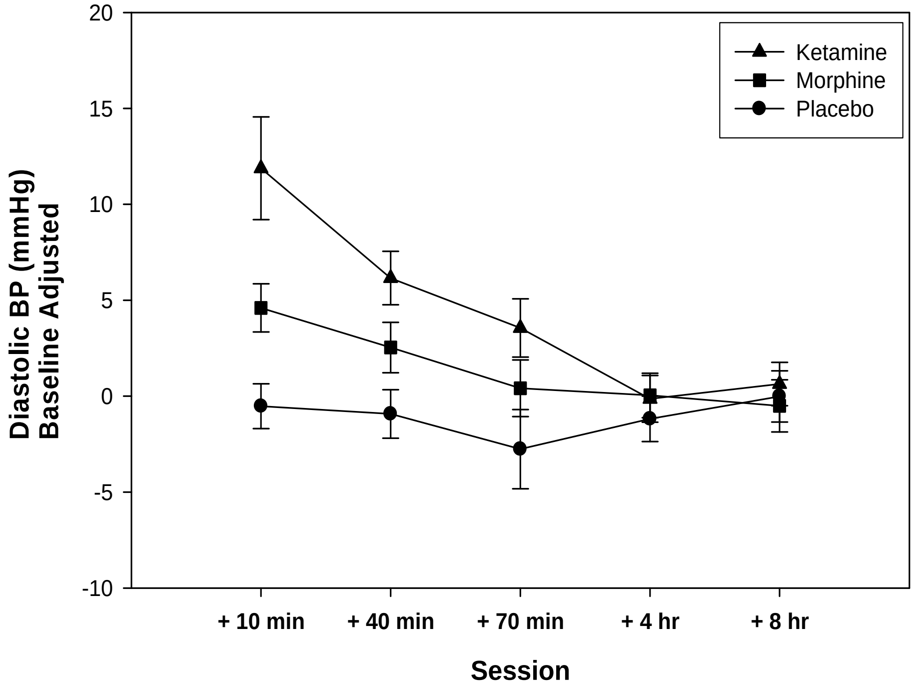


Figure 20. Diastolic blood pressure by drug and time session.

There was also a significant interaction between drug condition and session, F (4.213, 185.357) = 4.339, p = .002 (Greenhouse-Geisser corrected), observed power = .937. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the t-tests are presented in table 11. As shown in figure 20, during the +10 minute drug administration period, subjects' mean diastolic blood pressure in the ketamine condition was significantly higher than for the morphine and placebo conditions. In addition, during the same time period, subjects' mean diastolic blood pressure in the morphine condition was significantly higher than placebo. During the +40 minute drug administration period, subjects' mean diastolic blood pressure in the ketamine condition was significantly higher than placebo.

Table 11.
Post hoc results for diastolic blood pressure.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.001*
+40 minutes	ketamine vs. morphine	.116
	ketamine vs. placebo	.001*
	morphine vs. placebo	.044
+70 minutes	ketamine vs. morphine	.273
	ketamine vs. placebo	.112
	morphine vs. placebo	.406
+4 hours	ketamine vs. morphine	.615
	ketamine vs. placebo	.904
	morphine vs. placebo	.513
+8 hours	ketamine vs. morphine	.977
	ketamine vs. placebo	.427
	morphine vs. placebo	.489

* significant

Pulse

There was a significant main effect of session, F (3.284, 144.513) = 9.4, $p < .001$ (Greenhouse-Geisser corrected), observed power = .998. Pairwise comparisons revealed subjects' mean pulse increased significantly during the + 10 minute drug administration period compared to the other four sessions. There was also a significant main effect of drug condition, F (2, 88) = 7.447, $p = .001$, observed power = .935. Pairwise comparisons revealed subjects' mean pulse was significantly higher in the ketamine condition compared to the morphine condition ($p < .001$). The main effect of report time was not significant, F (2, 44) = 0.646, $p = .529$, observed power = .151.

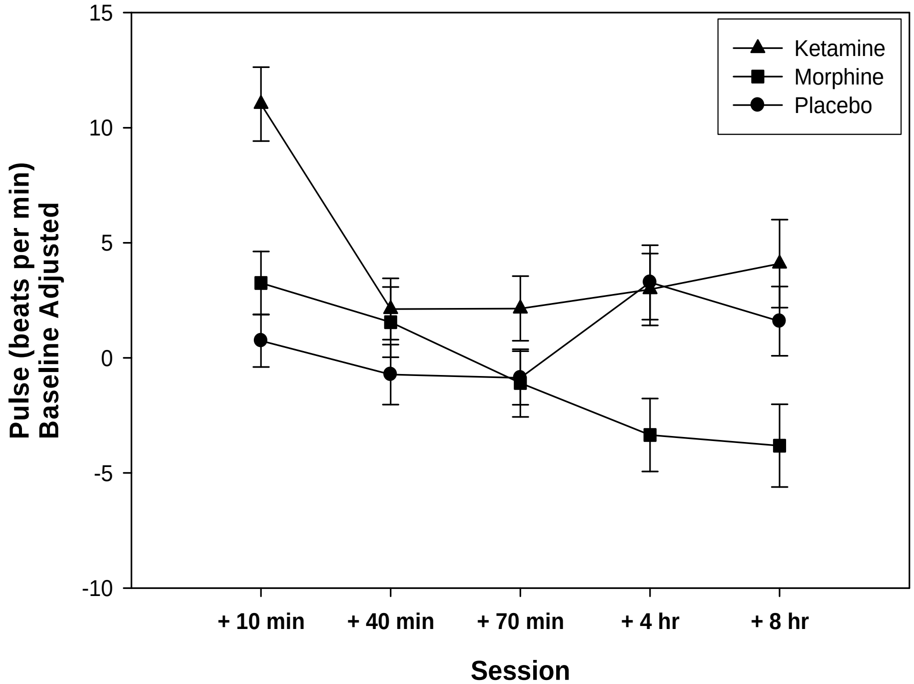


Figure 21. Pulse by drug and time session.

There was also a significant interaction between drug condition and session, F (8, 352) = 7.536, $p < .001$, observed power = 1.00. To investigate the significant interaction, paired *t*-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($\alpha = .05/15 = .003$). Results for the *t*-tests are presented in table 12. As shown in figure 21, during the +10 minute drug administration period, subjects' mean pulse in the ketamine condition was significantly higher than for the morphine and placebo conditions. In addition, subjects' mean pulse during the ketamine condition was significantly higher than the morphine condition at both the +4 hour and +8 hour drug administration periods. Finally, at the +8 hour drug administration period, subjects' mean pulse was significantly higher during the placebo condition than the morphine condition.

Table 12.
Post hoc results for pulse data.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.118
+40 minutes	ketamine vs. morphine	.877
	ketamine vs. placebo	.285
	morphine vs. placebo	.229
+70 minutes	ketamine vs. morphine	.067
	ketamine vs. placebo	.120
	morphine vs. placebo	.788
+4 hours	ketamine vs. morphine	< .001*
	ketamine vs. placebo	.716
	morphine vs. placebo	< .001
+8 hours	ketamine vs. morphine	< .001*
	ketamine vs. placebo	.445
	morphine vs. placebo	.001*

* significant (Bonferroni correction)

Temperature

There was a significant main effect of session, F (2.942, 129.444) = 4.642, p = .004 (Greenhouse-Geisser corrected), observed power = .880. Pairwise comparisons revealed that subjects mean temperature was greater during the +40 minute drug administration period than the +10 minute drug administration period (p < .001), and the +4 hour drug administration period (p = .026). The main effect of drug condition was not significant, F (2, 88) = 1.134, p = .326, observed power = .244. The main effect of report time was also not significant, F (2, 44) = 1.143, p = .328, observed power = .239.

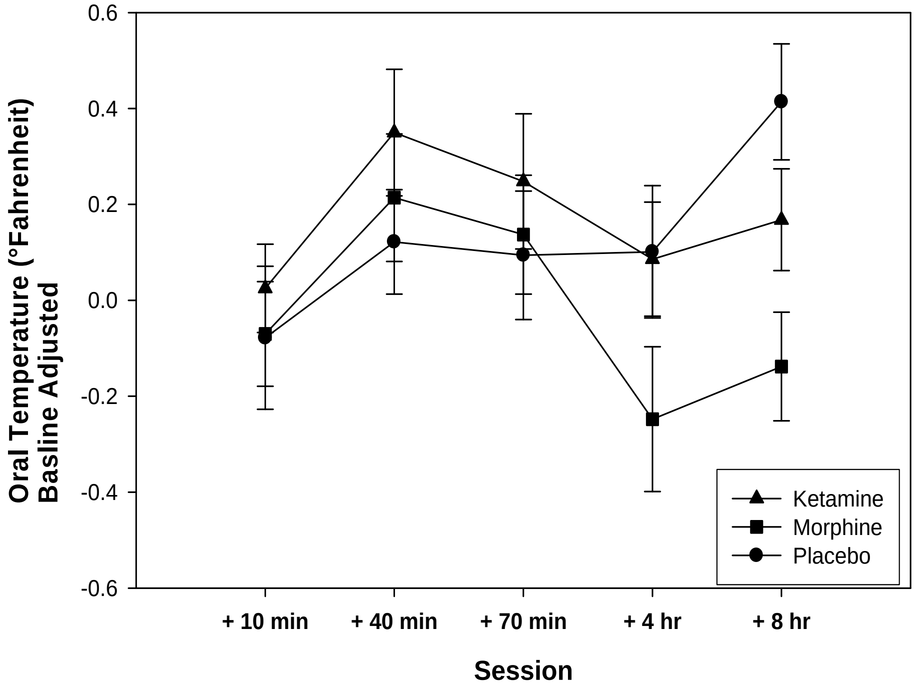


Figure 22. Temperature by drug and time session.

There was also a significant interaction between drug condition and session, F (5.828, 256.411) = 2.565, p = 0.021 (Greenhouse-Geisser corrected), observed power = .835. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = 0.05/15 = 0.003). Results for the t-tests are presented in table 13. As shown in figure 22, during the +8 hour drug administration period, subjects' mean temperature was significantly greater for the placebo condition than the morphine condition.

Table 13.
Post hoc results for temperature data.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	.790
	ketamine vs. placebo	.547
	morphine vs. placebo	.757
+40 minutes	ketamine vs. morphine	.500
	ketamine vs. placebo	.406
	morphine vs. placebo	.885
+70 minutes	ketamine vs. morphine	.510
	ketamine vs. placebo	.536
	morphine vs. placebo	.952
+4 hours	ketamine vs. morphine	.008
	ketamine vs. placebo	.989
	morphine vs. placebo	.016
+8 hours	ketamine vs. morphine	.008
	ketamine vs. placebo	.234
	morphine vs. placebo	< .001*

* significant (Bonferroni correction)

Respiration rate

The main effect of session was not significant, F (4, 168) = .320, p = .864, observed power = .121. The main effect of drug condition approached significance, F (2, 84) = 2.956, p = .057, observed power = .561. The main effect of report time was not significant, F (2, 42) = .899, p = .415, observed power = .195. The interaction between drug condition and session was also not significant, F (5.936, 249.326) = .873, p = .514 (Greenhouse-Geisser corrected), observed power = .341. Figure 23 presents respiratory rate data by drug and session.

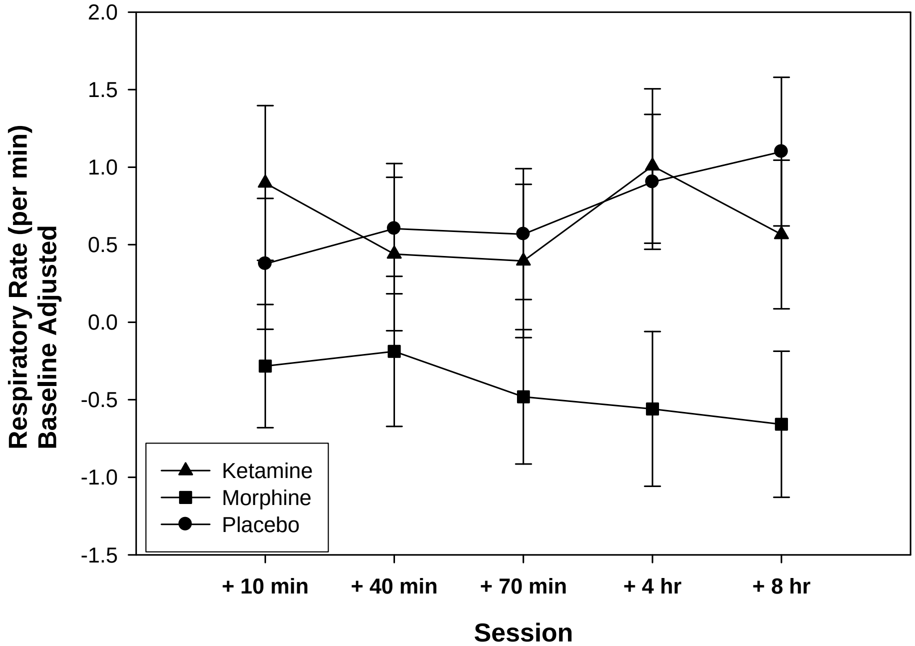


Figure 23. Respiratory rate by drug and time session.

<u>Oxygen saturation</u>

There was a significant main effect of session, F (4, 176) = 12.427, p < .001, observed power = 1.00. Pairwise comparisons revealed that subjects' mean oxygen saturation significantly increased during the +10 minute drug administration period compared to the +40 minute, +70 minute, and +4 hour periods. In addition, subjects mean oxygen saturation was significantly lower during the +70 minute drug administration period compared to the +8 hour drug administration period (p = .002). The main effect of drug condition was not significant, F (1.720, 75.694) = 0.581, p = .537 (Greenhouse-Geisser corrected), observed power = .137. The main effect of report time was not significant, F (2, 44) = 0.031, p = .969, observed power = .054. The interaction between drug condition and session was also not significant, F (8, 352) = 0.935, p = .488, observed power = .436. Figure 24 presents oxygen saturation data by drug and session.

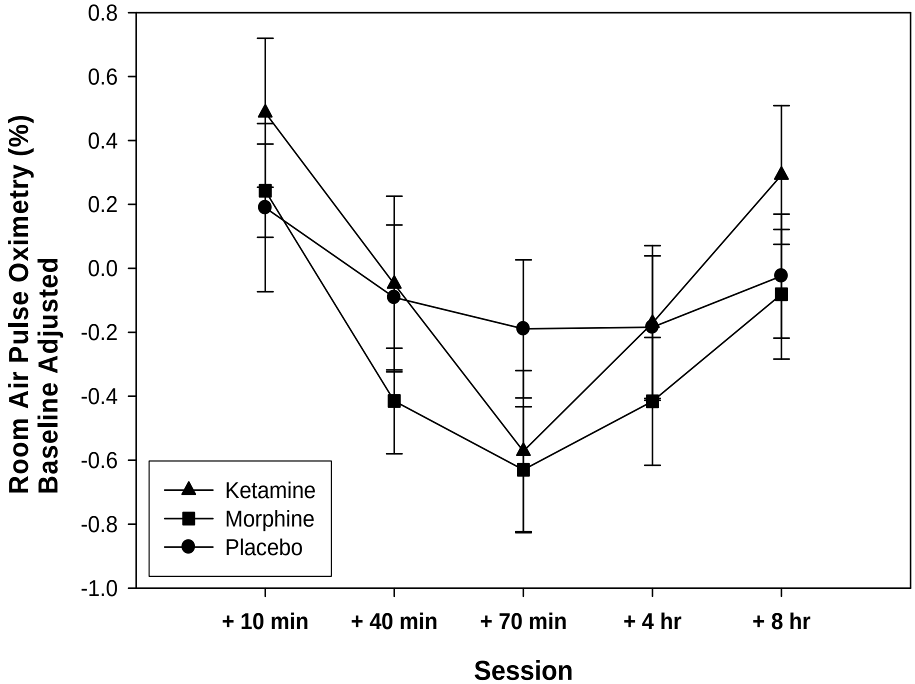


Figure 24. Oxygen saturation by drug and time session.

Symptom questionnaire

The Symptom Checklist (SC) data are comprised of 20 dependent measures (symptoms). Subjects were asked to complete the SC prior to dosing, as well as +10 minutes, +40 minutes, +70 minutes, +4 hours and +8 hours after being dosed. In some instances, data for a particular dependent measure were unavailable, mostly due to subject error while completing the questionnaire. Therefore, the sample sizes for each analysis differed. This information is presented in table 14.

Table 14.
Sample sizes for Symptom Checklist measures.

Measure	*n*
Nervousness	45
Feelings of excitement	45
Jitteriness	45
Feelings of aggression	46
Feelings of happiness/elation	43
Tiredness	45
Dizziness	46
Racing heartbeat	44
Pounding heart or heartbeat	44
Headache	45
Nausea	45
Vomiting	45
Tremor	45
Double vision	43
Blurred vision	45
Itching	44
Disordered thought processes	43
Poor concentration	44
Unreal thoughts	45
Any noticeable drug effect	37

Symptom rate

A frequency count was conducted to determine the number of subjects who reported a specific symptom, regardless of severity. This information is presented in table 15. The symptoms most commonly reported by subjects while experiencing ketamine were dizziness, poor concentration, and feelings of happiness. The most commonly reported symptoms by subjects experiencing morphine included tiredness, feelings of happiness, and nausea. The most commonly reported symptoms by subjects experiencing the placebo condition included feelings of happiness, nervousness, and tiredness. Regardless of severity, subjects reported more symptoms while experiencing ketamine than morphine or placebo. Subjects also had an option to record any additional symptoms verbatim if not included among the given list. These are tabulated in appendix B.

Table 15.
Most commonly reported symptoms by drug.

	ketamine						morphine						placebo					
	pre-dose	+10 min	+40 min	+70 min	+4 hrs	+8 hrs	pre-dose	+10 min	+40 min	+70 min	+4 hrs	+8 hrs	pre-dose	+10 min	+40 min	+70 min	+4 hrs	+8 hrs
Nervousness	0	2	3	0	0	0	4	4	0	0	0	0	3	3	1	0	0	0
Feelings of excitement	1	8	3	0	0	0	2	1	0	0	1	0	2	1	0	0	0	0
Jitteriness	1	10	11	4	0	0	0	6	7	6	5	1	1	1	2	1	0	0
Feelings of aggression	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Feelings of happiness/ elation	3	23	17	7	2	2	3	5	11	5	4	3	6	4	4	5	2	2
Tiredness	5	5	7	11	12	8	7	2	4	9	16	12	2	1	1	2	0	1
Dizziness	0	34	28	11	2	1	0	2	9	8	5	2	0	0	0	0	0	0
Racing heartbeat	0	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pounding heart or heartbeat	1	2	3	0	0	0	1	1	2	1	0	0	0	0	0	0	0	0
Headache	0	0	3	4	4	7	1	2	3	1	2	1	0	0	1	0	0	1
Nausea	1	2	9	7	3	1	0	2	2	6	11	8	0	1	1	1	0	1
Vomiting	0	1	2	0	0	0	0	0	0	2	4	3	0	0	0	0	0	0
Tremor	0	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Double vision	0	12	5	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Blurred vision	0	25	20	5	0	0	0	0	1	0	1	0	0	0	0	1	0	0
Itching	0	2	2	0	0	0	0	4	5	6	2	2	0	0	2	1	0	0
Disordered thought processes	0	22	17	3	0	0	0	0	2	4	0	0	0	0	1	0	0	0
Poor concentration	0	26	24	9	0	0	0	1	4	2	2	1	0	0	2	2	0	1
Unreal thoughts	0	3	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Any noticeable drug effect	0	47	39	23	6	1	0	13	21	19	8	1	0	1	3	3	0	0

Note: Numbers represent frequency count of subjects who reported a specific symptom, regardless of severity

Symptom severity

Subject responses to the SC were coded as follows: “no” = 0, “mild” =1, “moderate” = 2, “severe” = 3. The data were analyzed using 5 (session) x 3 (drug) repeated measures ANOVAs. The variable *session* was a within-subjects factor and its five levels were +10 minutes, +40 minutes, +70 minutes, +4 hours, and +8 hours. The scores were baseline corrected. The variable *drug condition* was also a within-subjects factor and its three levels were ketamine, morphine, and placebo.

Nervousness

There was a main effect of drug condition, F (1.741, 76.604) = 4.377, p = .02 (Greenhouse-Geisser corrected), observed power = .699. Pairwise comparisons revealed subjects’ mean nervousness scores were higher during the ketamine condition than during the morphine (p = .06) and placebo (p = .083) conditions.

The main effect of session was also significant, F (4, 176) = 6.534, p < .001, observed power = .990. Pairwise comparisons revealed subjects’ mean nervousness scores during the +10 minute drug administration period were higher than those during the +40 minute (p = .832), +70 minute (p = .061), + 4 hour (p = .061) and +8 hour (p = .061) drug administration periods.

The interaction between drug condition and session was not significant, F (8, 352) = 0.626, p = .756, observed power = .291. Figure 25 presents mean nervousness scores by drug and session.

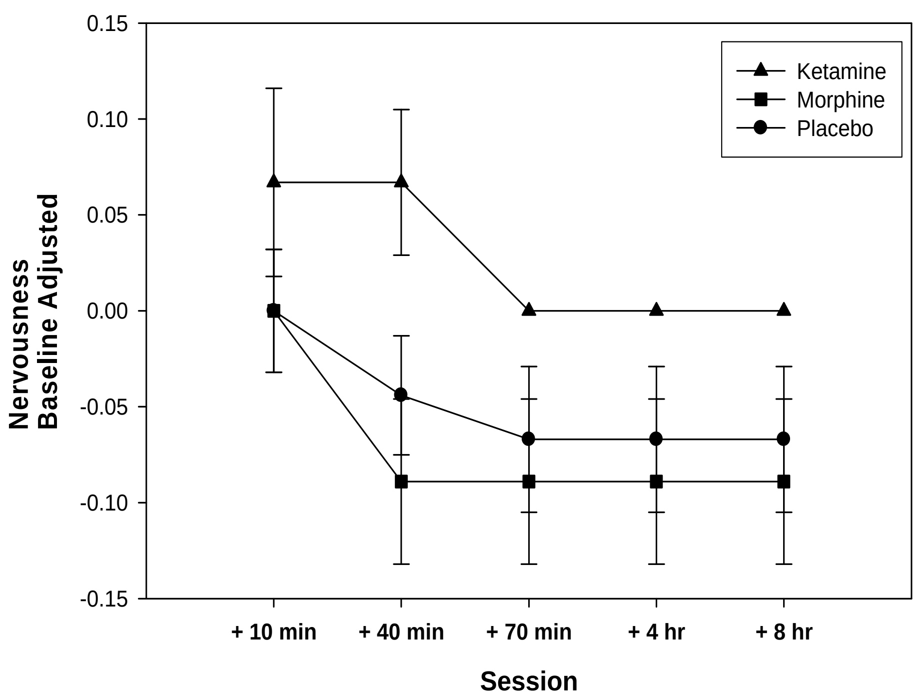


Figure 25. Mean nervousness scores by drug and time session.

Feelings of excitement

The main effect of drug condition was not significant, F (1.742, 76.642) = 2.140, p =.131 (Greenhouse-Geisser corrected), observed power = .397. However, there was a main effect of session, F (4, 176) = 7.817, $p < .001$, observed power = .997. Pairwise comparisons revealed that subjects' mean excitement scores were significantly higher during the +10 minute drug administration period compared to the +70 minute (p = .032), +4 hour (p = .034), and +8 hour (p = .032) periods. Figure 26 presents mean excitement scores by drug and session.

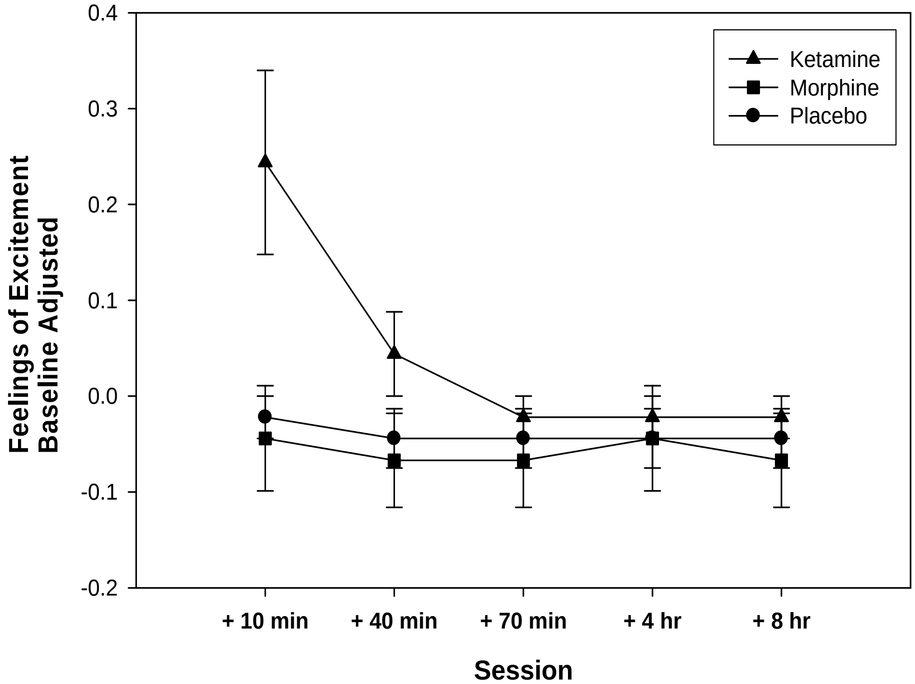


Figure 26. Mean excitement scores by drug and time session.

There was also a significant interaction between drug condition and session, F (8,352) = 5.274, $p < .001$, observed power = .999. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the t-tests are presented in table 16.

Table 16.
Post hoc results for excitement.

Session	Comparison	p
+10 minutes	ketamine vs. morphine	.008
	ketamine vs. placebo	.009
	morphine vs. placebo	.710
+40 minutes	ketamine vs. morphine	.096
	ketamine vs. placebo	.103
	morphine vs. placebo	.710
+70 minutes	ketamine vs. morphine	.420
	ketamine vs. placebo	.569
	morphine vs. placebo	.710
+4 hours	ketamine vs. morphine	.710
	ketamine vs. placebo	.569
	morphine vs. placebo	1.000
+8 hours	ketamine vs. morphine	.420
	ketamine vs. placebo	.569
	morphine vs. placebo	.710

Jitteriness

There was a main effect of drug condition, F (1.683, 74.071) = 7.442, p =.002 (Greenhouse-Geisser corrected), observed power = .900. Pairwise comparisons revealed subjects' mean jitteriness scores were significantly lower during the placebo condition compared to the ketamine (p = .005) and morphine (p =.02) conditions.

There was also a main effect of session, F (2.84, 124.95) = 6.443, p = .001 (Greenhouse-Geisser corrected), observed power = .959. Pairwise comparisons revealed subjects' mean jitteriness scores were significantly higher during the +10 minute drug administration period than the +8 hour period (p = .015). In addition, subjects' mean scores during the +40 minute period were significantly higher than those during the +4 hour (p =.002) and +8 hour (p = .002) periods. Figure 27 presents mean jitteriness scores by drug and session.

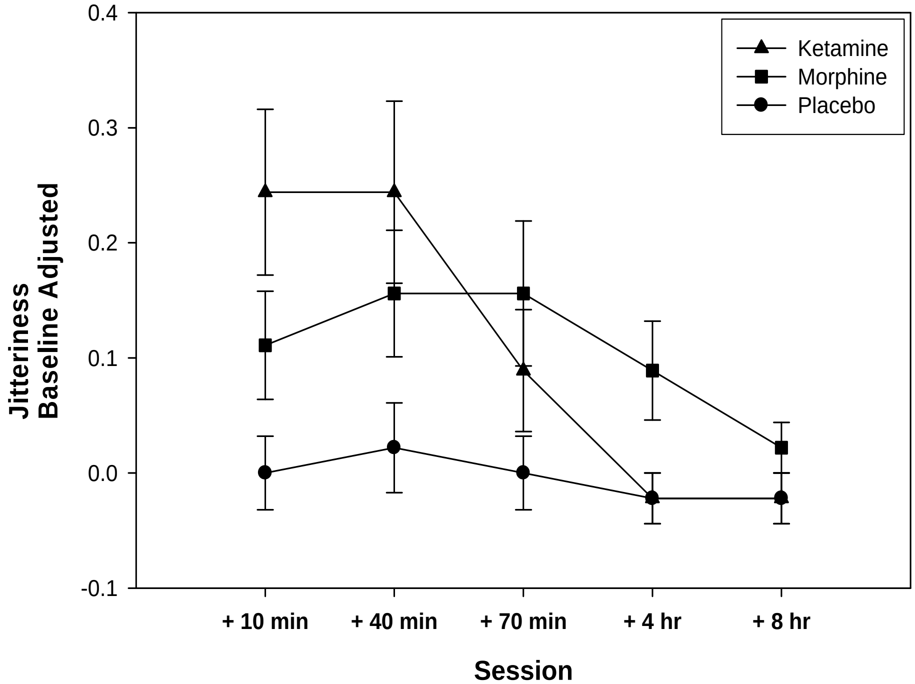


Figure 27. Mean jitteriness scores by drug and time session.

The interaction between drug condition and session was significant, F (8, 352) = 3.07, p = .002, observed power = .961. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the t-tests are presented in table 17. At the +10 minute drug administration period, subjects' mean jitteriness scores for the ketamine condition were significantly higher than the placebo condition.

Table 17.
Post hoc results for jitteriness.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	.168
	ketamine vs. placebo	.003*
	morphine vs. placebo	.032
+40 minutes	ketamine vs. morphine	.135
	ketamine vs. placebo	.009
	morphine vs. placebo	.057
+70 minutes	ketamine vs. morphine	.261
	ketamine vs. placebo	.160
	morphine vs. placebo	.018
+4 hours	ketamine vs. morphine	.018
	ketamine vs. placebo	-
	morphine vs. placebo	.018
+8 hours	ketamine vs. morphine	.160
	ketamine vs. placebo	-
	morphine vs. placebo	.160

* significant (Bonferroni correction)
- indicates no comparisons were performed as values were equal

Feelings of aggression

There were no significant main effects of drug condition, F (1.058, 47.618) = 0.804, p = .381 (Greenhouse-Geisser corrected), observed power = .145; or session, F (4,180) = 1.469, p = .213, observed power = .450. Also, the interaction between drug condition and session was not significant, F (8, 360) = 0.769, p = .630, observed power = .358. Figure 28 presents mean aggression scores by drug and session.

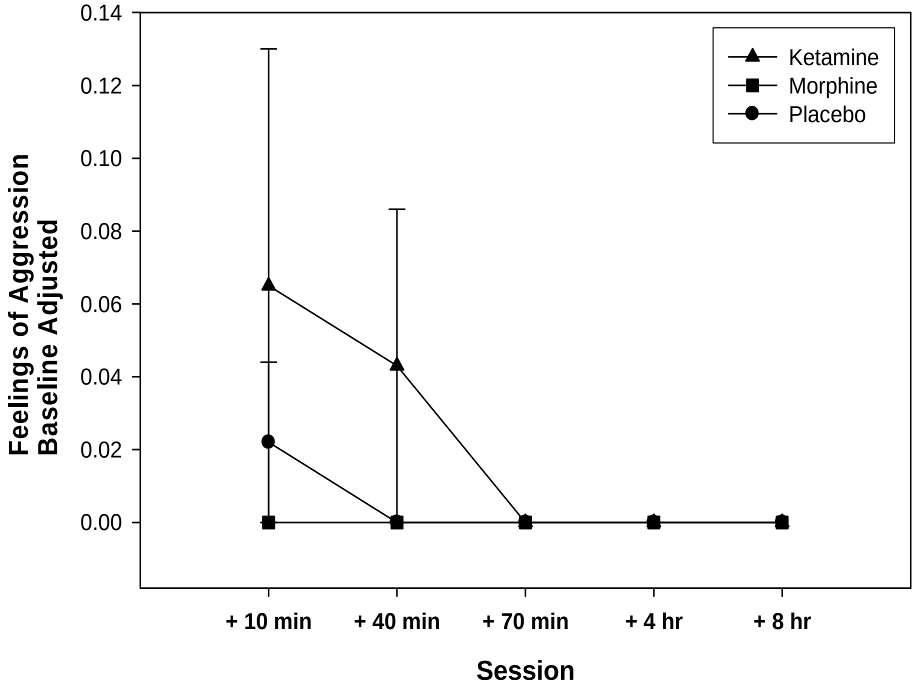


Figure 28. Mean aggression scores by drug and time session.

Feelings of happiness/elation

There was a significant main effect of drug condition, F (1.524, 64.002) = 10.87, $p < .001$ (Greenhouse-Gessier corrected), observed power = .967. Pairwise comparisons revealed subjects' mean happiness scores were significantly higher during the ketamine condition than during the morphine ($p = .012$) and placebo ($p = .002$) conditions.

There was also a significant main effect of session, F (4, 168) = 21.492, $p < .001$, observed power = 1.00. Pairwise comparison revealed subjects' mean happiness scores were significantly higher at the +10 minute drug administration period than at the +40 minute ($p =.042$), +70 minute ($p < .001$), +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Also, subjects' mean happiness scores were significantly higher at the +40 minute period than at the +70 minute ($p = .034$), + 4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Figure 29 presents mean happiness scores by drug and session.

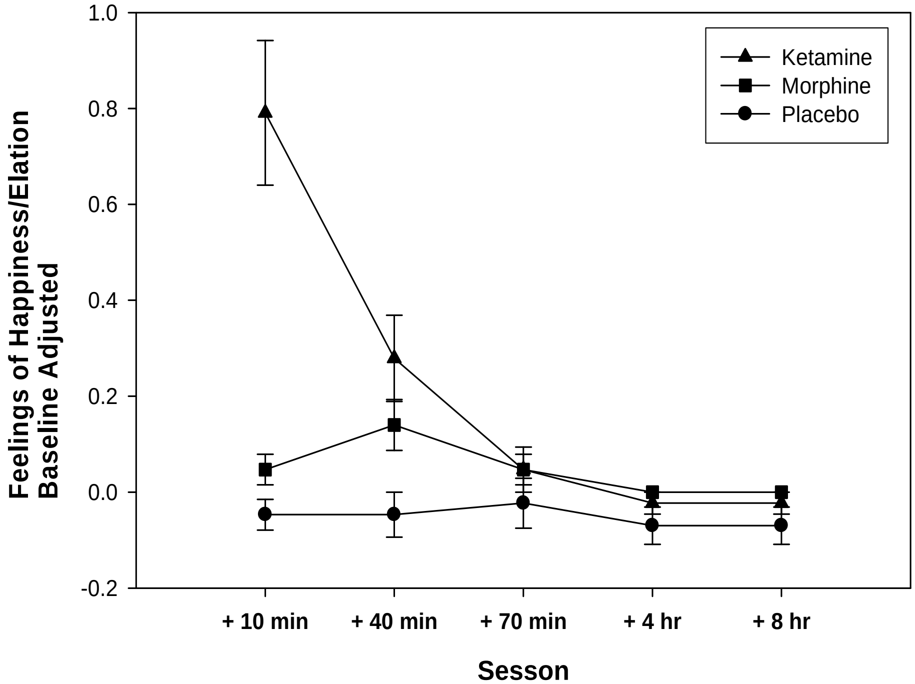


Figure 29. Mean happiness scores by drug and time session.

The interaction between drug condition and session was significant, F (8,336) = 18.632, $p <$ .001, observed power = 1.00. To investigate the significant interaction, paired *t*-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the *t*-tests are presented in table 18. During the +10 minute drug administration period, subjects' mean happiness scores in the ketamine condition were significantly higher than for the morphine and placebo conditions. In addition, subjects' mean happiness scores for the ketamine condition were significantly higher than placebo for the +40 minute drug administration period.

Table 18.
Post hoc results for happiness.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	<.001*
	ketamine vs. placebo	<.001*
	morphine vs. placebo	.044
+40 minutes	ketamine vs. morphine	.341
	ketamine vs. placebo	<.001*
	morphine vs. placebo	.004
+70 minutes	ketamine vs. morphine	1.000
	ketamine vs. placebo	.200
	morphine vs. placebo	.133
+4 hours	ketamine vs. morphine	.160
	ketamine vs. placebo	.183
	morphine vs. placebo	.058
+8 hours	ketamine vs. morphine	.323
	ketamine vs. placebo	.183
	morphine vs. placebo	.044

* significant (Bonferroni correction)

Tiredness

The main effect of drug condition was not significant, F (2, 88) = 2.134, p = .124, observed power = .427. There was a significant main effect of session, F (3.327, 146.403) = 6.303, p < .001 (Greenhouse-Gessier corrected), observed power = .974. Pairwise comparisons revealed subjects' mean tiredness scores during the +10 minute drug administration period were significantly lower than those during the +4 hour (p = .003) and +8 hour (p = .035) periods. Also, subjects' mean tiredness scores were significantly lower at the +40 minute period compared to the +4 hour period (p = .015). Figure 30 presents mean tiredness scores by drug and session.

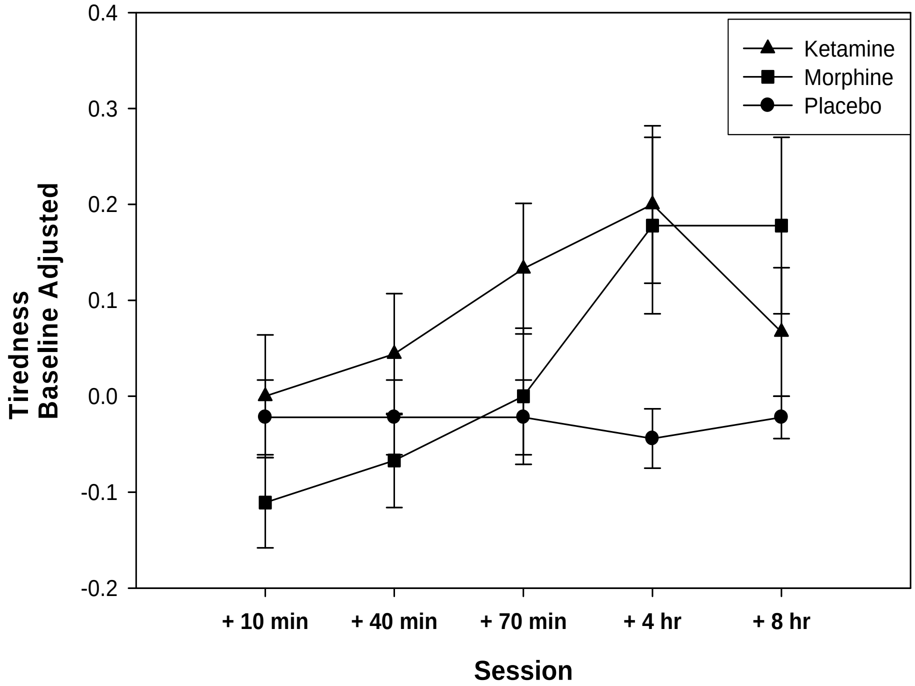


Figure 30. Mean tiredness scores by drug and time session.

The interaction between drug condition and session was also significant, F (4.454, 195.99) = 2.841, p = .021 (Greenhouse-Gessier corrected), observed power = .799. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the t-tests are presented in table 19.

Table 19.
Post hoc results for tiredness.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	.058
	ketamine vs. placebo	.767
	morphine vs. placebo	.160
+40 minutes	ketamine vs. morphine	.168
	ketamine vs. placebo	.323
	morphine vs. placebo	.485
+70 minutes	ketamine vs. morphine	.323
	ketamine vs. placebo	.110
	morphine vs. placebo	.598
+4 hours	ketamine vs. morphine	.607
	ketamine vs. placebo	.006
	morphine vs. placebo	.007
+8 hours	ketamine vs. morphine	.224
	ketamine vs. placebo	.209
	morphine vs. placebo	.024

Dizziness

There was a significant main effect of drug condition, F (1.715, 77.195) = 54.190, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. Pairwise comparisons revealed subjects reported significantly higher dizziness scores during the ketamine condition than during the morphine ($p < .001$) and placebo ($p < .001$) conditions. Also, subjects reported significantly higher dizziness scores during the morphine condition compared to the placebo condition (p = .004).

The main effect of session was also significant, F (2.761, 124.267) = 32.442, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. Pairwise comparison revealed subjects' mean dizziness scores were significantly higher at the +10 minute drug administration period than at the +70 minute ($p < .001$), +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Also, subjects' mean dizziness scores were significantly higher at the +40 minute period than at the +70 minute ($p < .001$), +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Lastly, subjects' mean dizziness scores during the +70 minute period were significantly higher than those during the +8 hour period (p = .006). Figure 31 presents mean dizziness scores by drug and session.

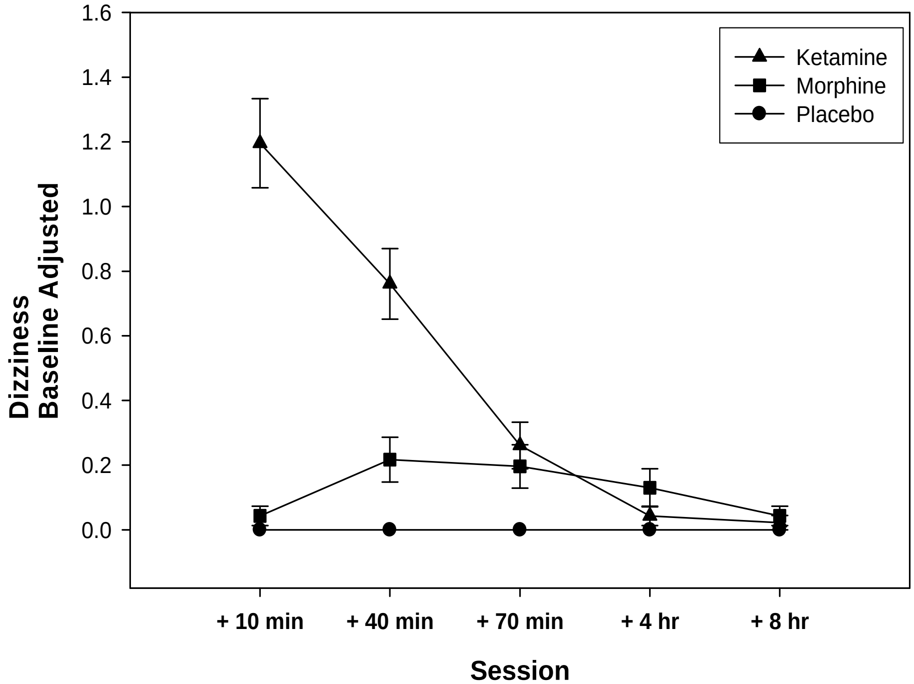


Figure 31. Mean dizziness scores by drug and time session.

The interaction between drug condition and session was also significant, F (3.221, 144.934) = 35.212, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($\alpha = .05/15 = .003$). Results for the t-tests are presented in table 20. During the +10 minute drug administration period, subjects' dizziness scores in the ketamine condition were significantly higher than for the morphine and placebo conditions. In addition, mean dizziness scores for the ketamine condition were significantly higher than those of morphine and placebo for the +40 minute drug administration period. During the same time period, dizziness ratings for the morphine condition were significantly higher than the placebo condition. Lastly, subjects' mean dizziness scores for the ketamine condition were significantly higher than placebo for the +70 minute period.

Table 20.
Post hoc results for dizziness.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.160
+40 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.003*
+70 minutes	ketamine vs. morphine	.371
	ketamine vs. placebo	.001*
	morphine vs. placebo	.005
+4 hours	ketamine vs. morphine	.103
	ketamine vs. placebo	.160
	morphine vs. placebo	.032
+8 hours	ketamine vs. morphine	.569
	ketamine vs. placebo	.323
	morphine vs. placebo	.160

* significant (Bonferroni correction)

Racing heartbeat

There were no significant main effects of drug condition, F (2, 86) = 1.834, p = .166, observed power = .373) or session (F (4, 172) = 1.623, p = .171, observed power = .493. Also, the interaction between drug condition and session was not significant, F (8, 344) = 1.623, p = .117, observed power = .715. Figure 32 presents mean racing heartbeat scores by drug and session.

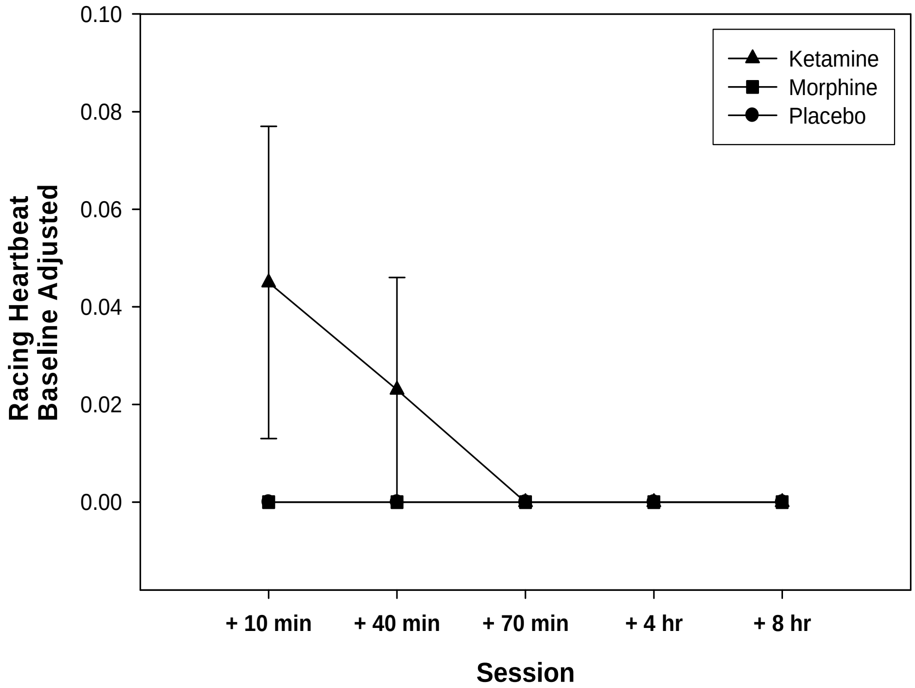


Figure 32. Mean racing heartbeat scores by drug and time session.

Pounding heart or heartbeat

The main effect of drug condition was not significant, F (1.760, 75.669) = 1.639, p = .204 (Greenhouse-Geisser corrected), observed power = .315. The main effect of session was significant, F (4, 172) = 2.806, p = .027, observed power = .759. Pairwise comparisons revealed subjects' mean ratings during the +40 minute drug administration period were higher than the +4 hour (p = .568) and the +8 hour (p =.568) periods.

The interaction between drug condition and session was not significant, F (8, 344) = 1.334, p = .225, observed power = .610. Figure 33 presents mean pounding heartbeat scores by drug and session.

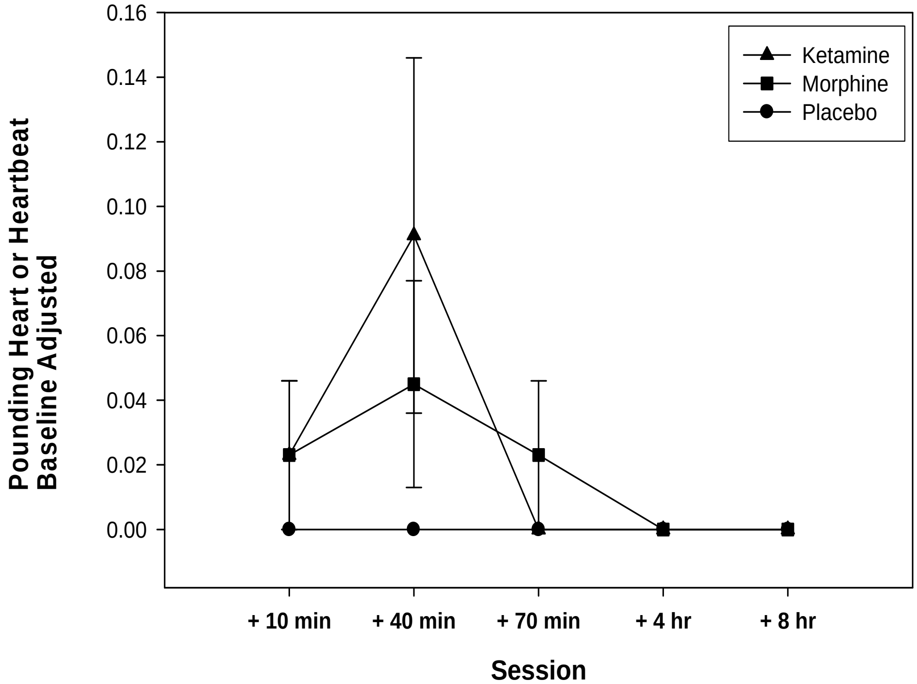


Figure 33. Mean pounding heartbeat scores by drug and time session.

Headache

There was a significant main effect of drug condition, *F* (1.688, 74.262) = 3.336, *p* = .049 (Greenhouse-Geisser corrected), observed power = .566. Pairwise comparisons revealed subjects' mean headache scores were higher under the ketamine condition compared to the morphine (*p* = .211) and placebo (*p* = .083) conditions.

The main effect of session was not significant, *F* (3.142, 138.259) = 1.666, *p* = .175 (Greenhouse-Geisser corrected), observed power = .440; as well as the interaction between drug condition and session, *F* (4.932, 217.026) = 1.474, *p* = .20 (Greenhouse-Geisser corrected), observed power = .509. Figure 34 presents mean headache scores by drug and session.

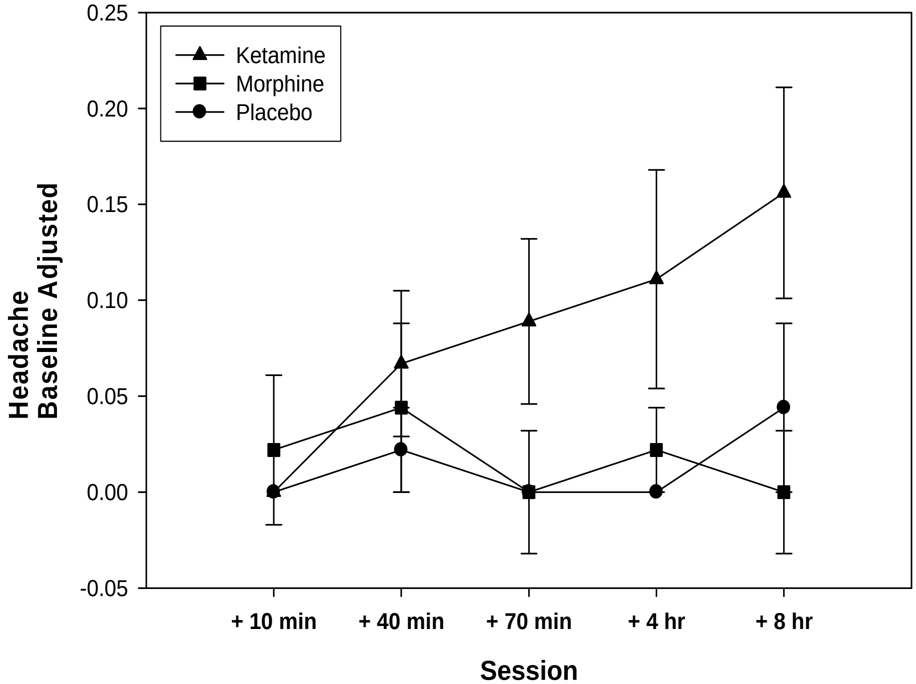


Figure 34. Mean headache scores by drug and time session.

Nausea

There were no significant main effects of drug condition, F (1.597, 70.283) = 2.655, p = .089 (Greenhouse-Geisser corrected), observed power = .456) or session (F (3.173, 139.592) = 1.218, p = .306 (Greenhouse-Geisser corrected), observed power = .331. Figure 35 presents mean nausea scores by drug and session. However, the interaction between drug condition and session was significant, F (8, 352) = 4.605, $p < .001$, observed power = .997. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the t-tests are presented in table 21. At the +4 hour drug administration period, subjects' mean nausea scores under the morphine condition were significantly higher than the placebo condition.

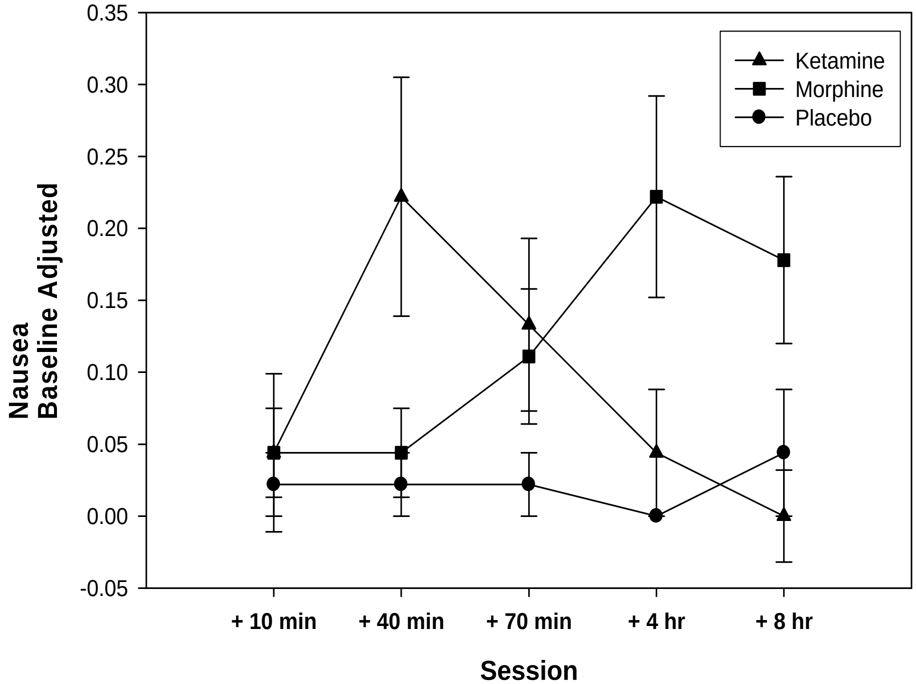


Figure 35. Mean nausea scores by drug and time session.

Table 21.
Post hoc scores for nausea.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	1.000
	ketamine vs. placebo	.710
	morphine vs. placebo	.569
+40 minutes	ketamine vs. morphine	.058
	ketamine vs. placebo	.018
	morphine vs. placebo	.569
+70 minutes	ketamine vs. morphine	1.000
	ketamine vs. placebo	.096
	morphine vs. placebo	.024
+4 hours	ketamine vs. morphine	.006
	ketamine vs. placebo	.323
	morphine vs. placebo	.001*
+8 hours	ketamine vs. morphine	.010
	ketamine vs. placebo	.420
	morphine vs. placebo	.083

* significant (Bonferroni correction)

Vomiting

There were no significant main effects of drug condition, F (2, 88) = 1.894, p = .157, observed power = .384) or session (F (2.954, 129.993) = 0.454, p = .712 (Greenhouse-Geisser corrected), observed power = .139. Figure 36 presents mean vomit scores by drug and session. However, the interaction between drug condition and session was significant, F(8, 352) = 1.977, p =.048, observed power = .814. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the t-tests are presented in table 22.

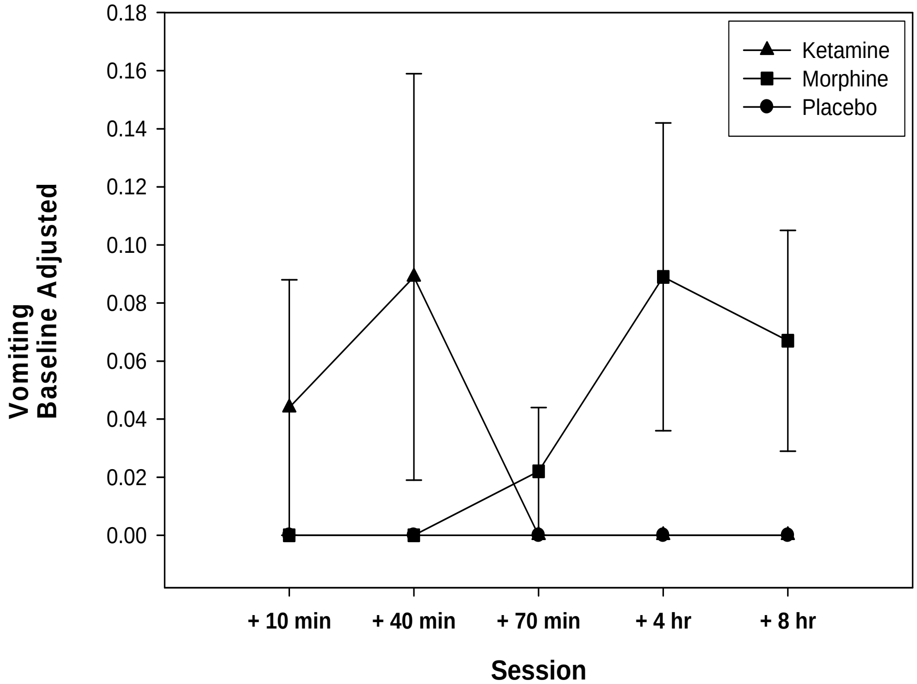


Figure 36. Mean vomiting scores by drug and time session.

Table 22.
Post hoc results for vomiting.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	.323
	ketamine vs. placebo	.323
	morphine vs. placebo	-
+40 minutes	ketamine vs. morphine	.209
	ketamine vs. placebo	.209
	morphine vs. placebo	-
+70 minutes	ketamine vs. morphine	.160
	ketamine vs. placebo	-
	morphine vs. placebo	.160
+4 hours	ketamine vs. morphine	.058
	ketamine vs. placebo	-
	morphine vs. placebo	.058
+8 hours	ketamine vs. morphine	.083
	ketamine vs. placebo	-
	morphine vs. placebo	.083

- indicates no comparisons were performed as values were equal

Tremor

There were no significant main effects of drug condition, F (1.323, 58.224) = 1.413, p = .247 (Greenhouse-Geisser corrected), observed power = .242) or session (F (4,176) = 0.71, p = .586, observed power = .227. Also, the interaction between drug condition and session was not significant, F (8, 352) = 0.796, p = .606, observed power = .371. Figure 37 presents mean tremor scores by drug and session.

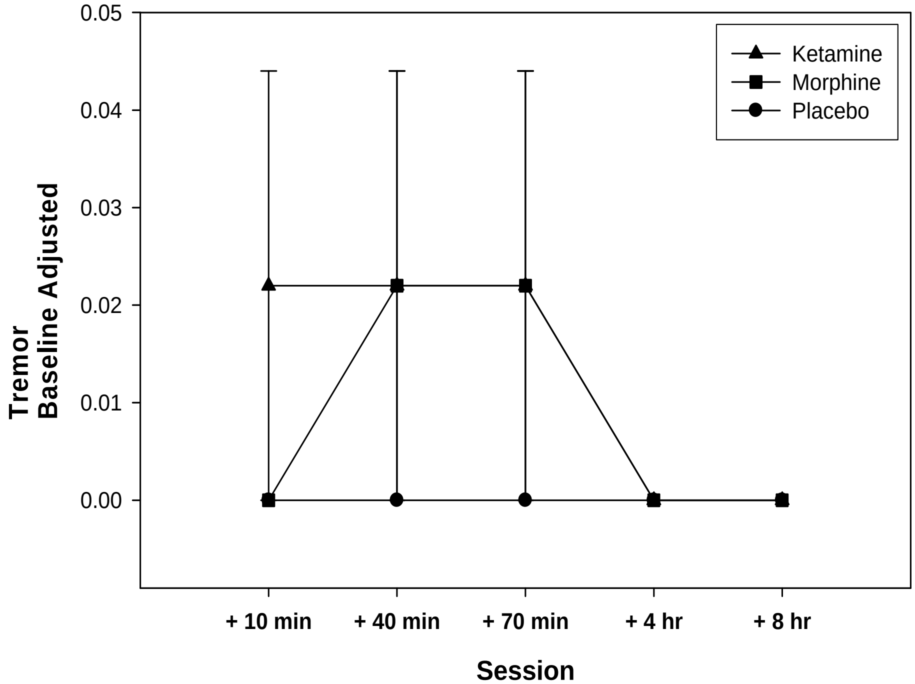


Figure 37. Mean tremor scores by drug and time session.

Double vision

The main effect of drug condition was significant, F (2, 84) = 10.096, p < .001, observed power = .983. Pairwise comparisons revealed that overall, subjects' mean double vision score was greater for the ketamine condition than the morphine (p = .008) and placebo (p = .008) conditions.

The main effect of session was also significant, F (4, 168) = 5.938, p < .001, observed power = .983. Pairwise comparisons revealed that subjects' mean double vision score was significantly greater during the +10 minute drug administration period than the +4 hour (p = .018) and +8 hour (p = .018) periods. Figure 38 presents mean double vision scores by drug and session.

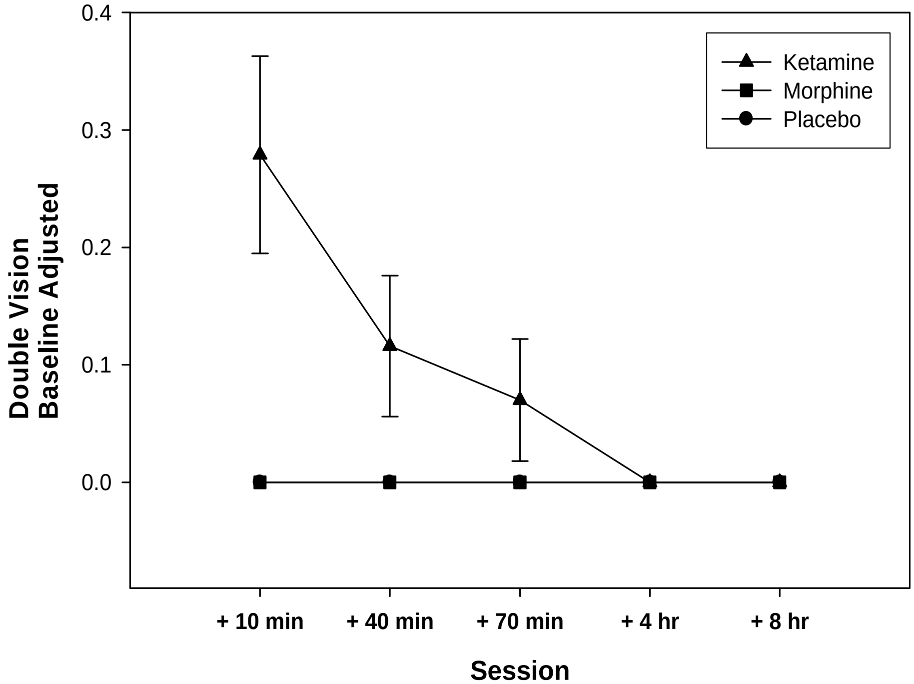


Figure 38. Mean double vision scores by drug and time session.

The interaction between drug condition and session was also significant, F (8, 336) = 5.938, $p < .001$, observed power = 1.00. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($\alpha = .05/15 = .003$). Results for the t-tests are presented in table 23. During the +10 minute drug administration period, subjects' mean double vision scores in the ketamine condition were significantly higher than for the morphine and placebo conditions.

Table 23.
Post hoc results for double vision.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	-
+40 minutes	ketamine vs. morphine	.058
	ketamine vs. placebo	.058
	morphine vs. placebo	-
+70 minutes	ketamine vs. morphine	.183
	ketamine vs. placebo	.183
	morphine vs. placebo	-
+4 hours	ketamine vs. morphine	-
	ketamine vs. placebo	-
	morphine vs. placebo	-
+8 hours	ketamine vs. morphine	-
	ketamine vs. placebo	-
	morphine vs. placebo	-

* significant (Bonferroni correction)
- indicates no comparisons were performed as values were equal

Blurred vision

The main effect of drug condition was significant, F (1.047, 46.068) = 38.160, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. Pairwise comparisons revealed that, overall, subjects' mean blurred vision score was greater for the ketamine condition than the morphine ($p < .001$) and placebo ($p < .001$) conditions.

The main effect of session was also significant, F (1.723, 75.799) = 23.990, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. Pairwise comparison revealed subjects' mean blurred vision scores were significantly higher at the +10 minute drug administration period than at the +70 minute ($p < .001$), +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Also, mean blurred vision scores were significantly higher at the +40 minute period than at the +70 minute ($p = .003$), + 4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Figure 39 presents mean blurred vision scores by drug and session.

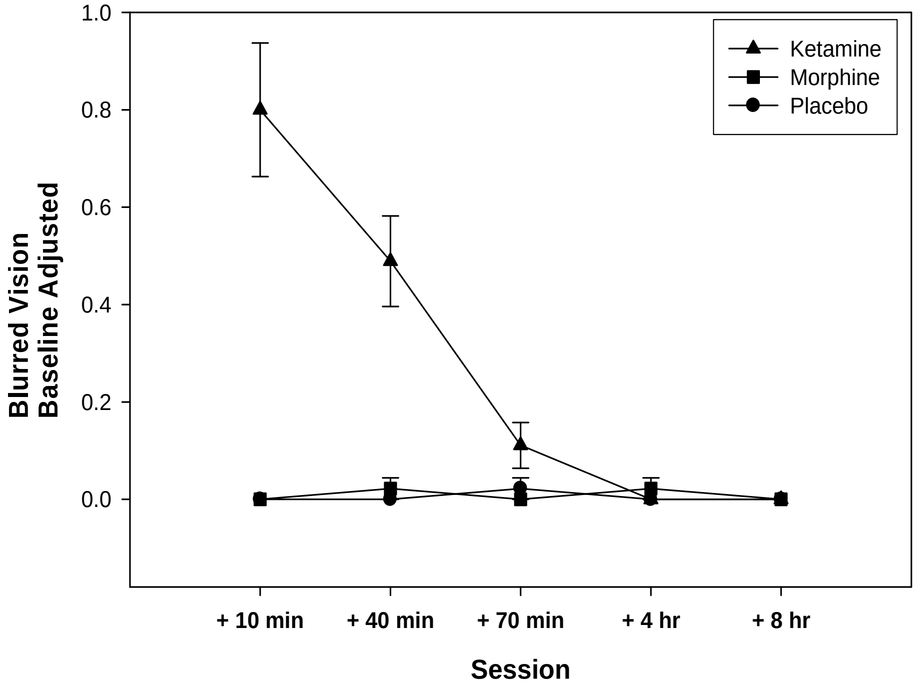


Figure 39. Mean blurred vision scores by drug and time session.

The interaction between drug condition and session was also significant, F (8, 352) = 23.828, $p < .001$, observed power = 1.00. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the t-tests are presented in table 24. During the +10 minute drug administration period, subjects' mean blurred vision scores in the ketamine condition was significantly higher than for the morphine and placebo conditions. In addition, during the +40 minute period, mean blurred vision scores in the ketamine condition was significantly higher than for the morphine and placebo conditions.

Table 24.
Post hoc results for blurred vision.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	-
+40 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.323
+70 minutes	ketamine vs. morphine	.024
	ketamine vs. placebo	.103
	morphine vs. placebo	.323
+4 hours	ketamine vs. morphine	.323
	ketamine vs. placebo	-
	morphine vs. placebo	.323
+8 hours	ketamine vs. morphine	-
	ketamine vs. placebo	-
	morphine vs. placebo	-

* significant (Bonferroni correction)
- indicates no comparisons were performed as values were equal

Itching

The main effect of drug condition was significant, F (1.249, 53.669) = 5.513, p = .016 (Greenhouse-Geisser corrected), observed power = .699. Pairwise comparisons revealed that overall, subjects' mean itching score was higher for the morphine condition than the ketamine (p = .052) and placebo (p = .061) conditions. Figure 40 presents mean itching scores by drug and session.

The main effect of session was not significant, F (2.590, 111.378) = 1.246, p = .296 (Greenhouse-Geisser corrected), observed power = .302; as well as the interaction between drug condition and session, F (8, 344) = 0.37, p = .936, observed power = .176.

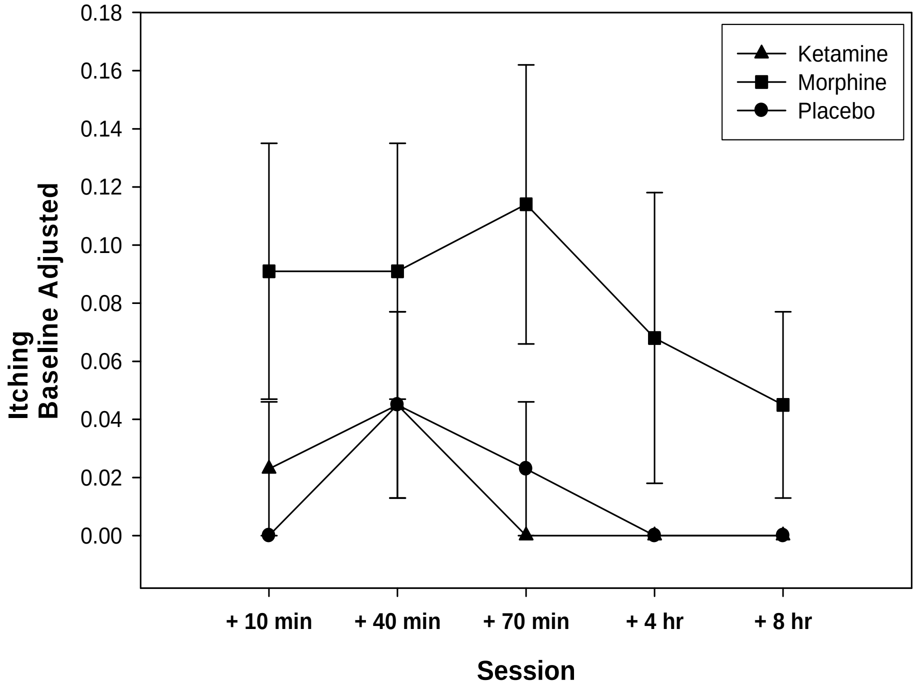


Figure 40. Mean itching scores by drug and time session.

Disordered thought processes

The main effect of drug condition was significant, F (1.115, 46.831) = 21.323, $p < .001$ (Greenhouse-Geisser corrected), observed power = .997. Pairwise comparisons revealed that, overall, subjects' mean disordered thought score was greater for the ketamine condition than the morphine ($p < .001$) and placebo ($p < .001$) conditions.

The main effect of session was also significant, F (4, 168) = 17.064, $p < .001$, observed power = 1.00. Pairwise comparison revealed subjects' mean disordered thought scores were significantly higher at the +10 minute drug administration period than at the +70 minute (p = .002), +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Also, mean scores were significantly higher at the +40 minute period than at the +70 minute (p = .035), +4 hour (p = .001) and +8 hour (p = .001) periods. Figure 41 presents mean disordered thought scores by drug and session.

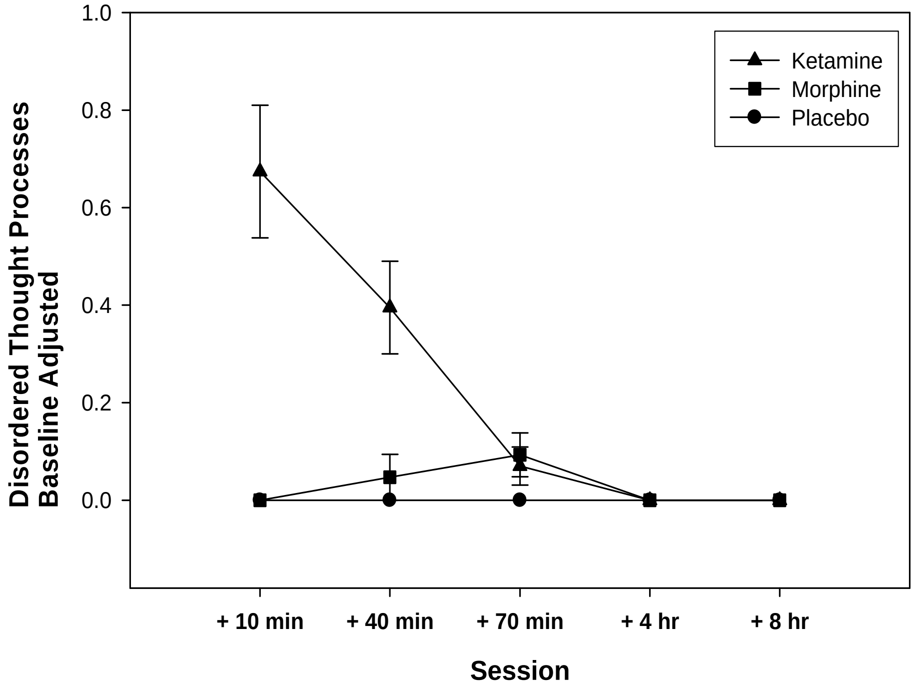


Figure 41. Mean disordered thought scores by drug and time session.

The interaction between drug condition and session was also significant, *F* (8, 336) = 16.114, *p* < .001, observed power = 1.00. To investigate the significant interaction, paired *t*-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied (α = .05/15 = .003). Results for the *t*-tests are presented in table 25. During the +10 minute drug administration period, subjects' disordered thought scores in the ketamine condition were significantly higher than for the morphine and placebo conditions. In addition, during the +40 minute period, scores in the ketamine condition was significantly higher than for the morphine and placebo conditions.

Table 25.
Post hoc results for disordered thought.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	-
+40 minutes	ketamine vs. morphine	.001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.323
+70 minutes	ketamine vs. morphine	.710
	ketamine vs. placebo	.083
	morphine vs. placebo	.044
+4 hours	ketamine vs. morphine	-
	ketamine vs. placebo	-
	morphine vs. placebo	-
+8 hours	ketamine vs. morphine	-
	ketamine vs. placebo	-
	morphine vs. placebo	-

* significant (Bonferroni correction)
- indicates no comparisons were performed as values were equal

Poor concentration

The main effect of drug condition was significant, F (1.212, 52.126) = 32.783, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. Pairwise comparisons revealed that, overall, subjects' mean poor concentration score was greater for the ketamine condition than the morphine ($p < .001$) and placebo ($p < .001$) conditions.

The main effect of session was also significant, F (2.405, 103.406) = 21.822, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. Pairwise comparison revealed subjects' mean poor concentration scores were significantly higher at the +10 minute drug administration period than at the +70 minute ($p = .001$), +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Also, mean scores were significantly higher at the +40 minute drug administration period than at the +70 minute ($p = .027$), +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Lastly, scores at the +70 minute drug administration period were significantly greater than those at the +4 hour ($p = .033$) and +8 hour ($p = .033$) periods. Figure 42 presents mean poor concentration scores by drug and session.

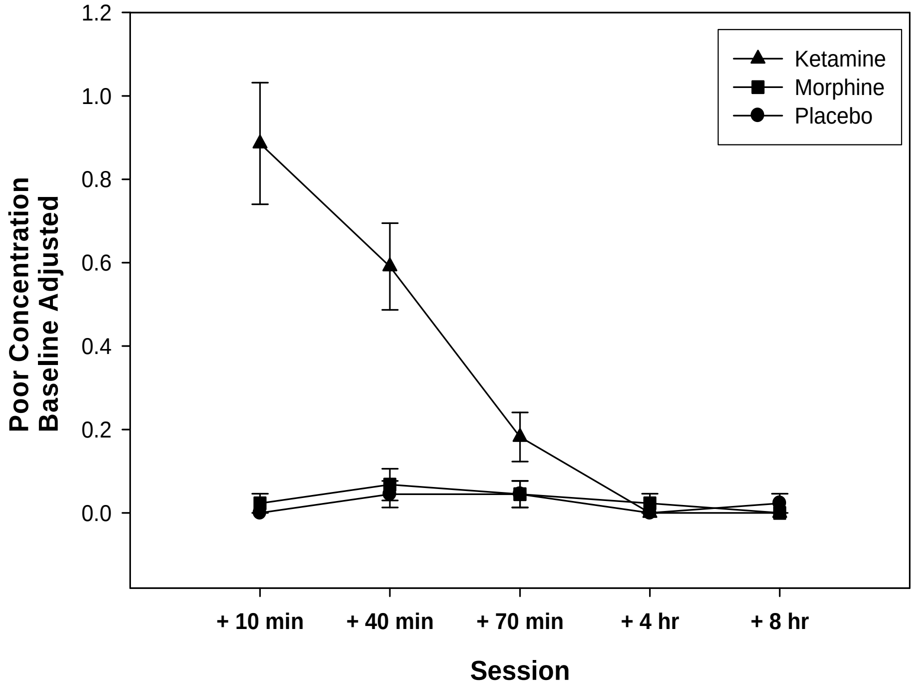


Figure 42. Mean poor concentration scores by drug and time session.

The interaction between drug condition and session was also significant, *F* (2.48, 106.653) = 22.94, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. To investigate the significant interaction, paired *t*-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($\alpha = .05/15 = .003$). Results for the *t*-tests are presented in table 26. During the +10 minute drug administration period, subjects' poor concentration scores in the ketamine condition were significantly higher than for the morphine and placebo conditions. In addition, during the +40 minute period, scores in the ketamine condition were significantly higher than for the morphine and placebo conditions.

Table 26.
Post hoc results for poor concentration.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.323
+40 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	.323
+70 minutes	ketamine vs. morphine	.033
	ketamine vs. placebo	.018
	morphine vs. placebo	1.000
+4 hours	ketamine vs. morphine	.323
	ketamine vs. placebo	-
	morphine vs. placebo	.323
+8 hours	ketamine vs. morphine	.323
	ketamine vs. placebo	.323
	morphine vs. placebo	1.000

* significant (Bonferroni correction)
- indicates no comparisons were performed as values were equal

Unreal thoughts

There were no significant main effects of drug condition, F (1.071, 47. 102) = 1.998, p = .163 (Greenhouse-Geisser corrected), observed power = .292; or session, F (4,176) = 1.499, p = .204, observed power = .458. Also, the interaction between drug condition and session was not significant, F (8, 352) = 1.608, p = .121, observed power = .710. Figure 43 presents mean unreal thoughts scores by drug and session.

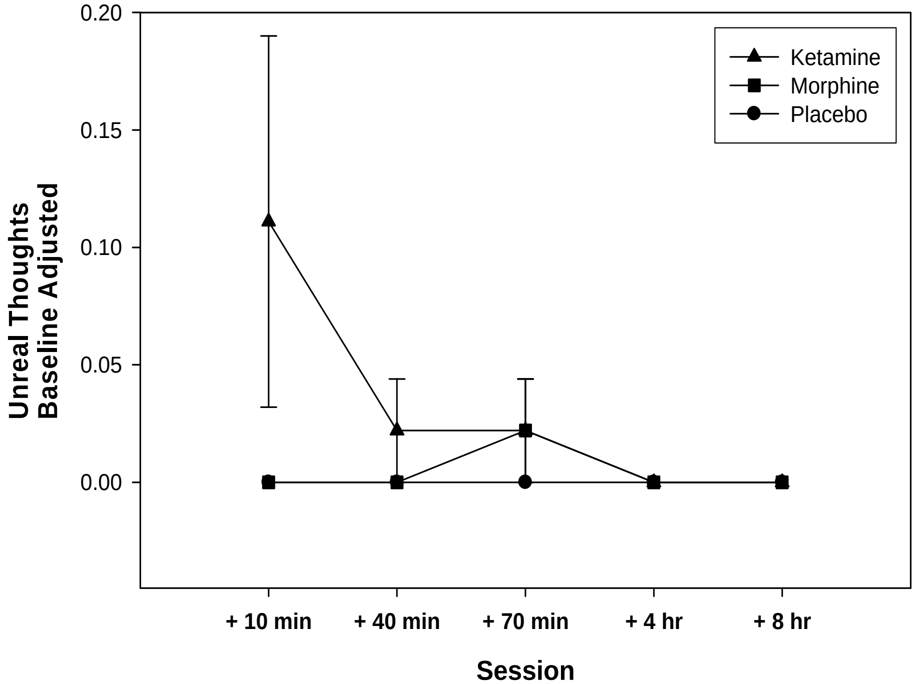


Figure 43. Mean unreal thoughts scores by drug and time session.

Any noticeable drug effect

The main effect of drug condition was significant, F (2, 72) = 120.51, $p < .001$, observed power = 1.00. Pairwise comparisons revealed that, overall, subjects' mean drug effect score was greater for the ketamine condition than the morphine ($p < .001$) and placebo ($p < .001$) conditions. Also, subjects reported significantly higher scores during the morphine condition compared to the placebo condition ($p < .001$).

The main effect of session was also significant, F (2.786, 100.283) = 82.081, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. Pairwise comparison revealed subjects' mean drug effect scores were significantly higher at the +10 minute drug administration period than at the + 40 minute (p = .001), +70 minute ($p < .001$), +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Also, subjects' mean scores were significantly higher at the +40 minute drug administration period than at the +70 minute ($p < .001$), + 4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Lastly, scores at the +70 minute drug administration period were significantly greater than those at the +4 hour ($p < .001$) and +8 hour ($p < .001$) periods. Figure 44 presents mean drug effect scores by drug and session.

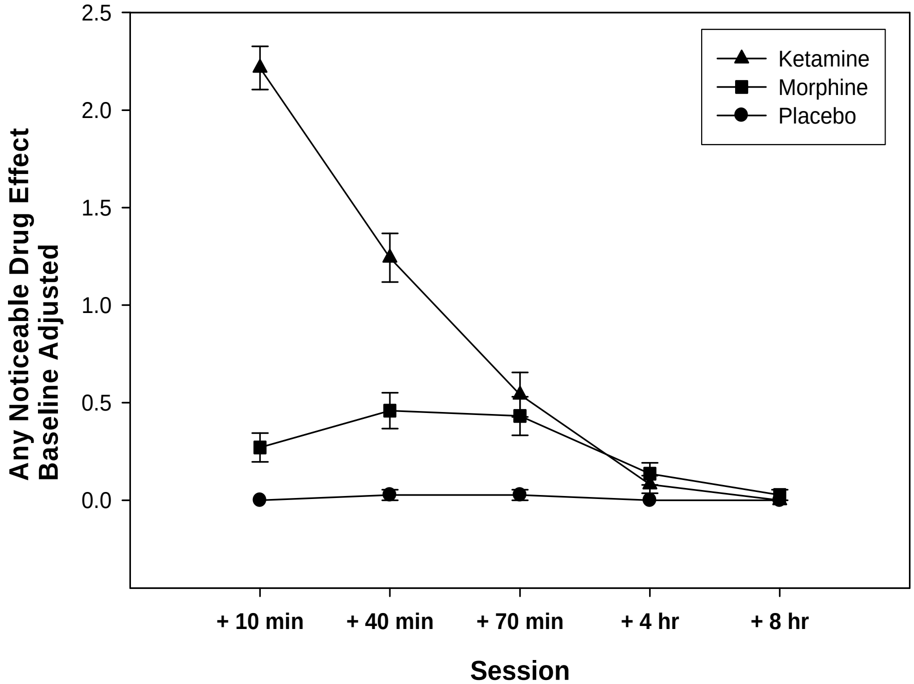


Figure 44. Mean drug effect scores by drug and time session.

The interaction between drug condition and session was also significant, F (4.509, 162.322) = 84.443, $p < .001$ (Greenhouse-Geisser corrected), observed power = 1.00. To investigate the significant interaction, paired t-tests were conducted. To reduce the risk of a Type I error, a Bonferroni correction was applied ($\alpha = .05/15 = .003$). Results for the t-tests are presented in table 27. During the +10 minute drug administration period, subjects' poor concentration scores in the ketamine condition were significantly higher than for the morphine and placebo conditions. At the same time session, scores for the morphine condition were significantly higher than placebo. In addition, during the +40 minute period, subjects' scores in the ketamine condition was significantly higher than for the morphine and placebo conditions. At the same time session, scores for the morphine condition were significantly higher than placebo. Finally, at the +70 minute period, subjects mean drug effect scores for placebo were significantly less than those for the ketamine and morphine conditions.

Table 27.
Post hoc results for drug effect.

Session	Comparison	*p*
+10 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	< .001*
+40 minutes	ketamine vs. morphine	< .001*
	ketamine vs. placebo	< .001*
	morphine vs. placebo	< .001*
+70 minutes	ketamine vs. morphine	.323
	ketamine vs. placebo	< .001*
	morphine vs. placebo	< .001*
+4 hours	ketamine vs. morphine	.421
	ketamine vs. placebo	.044
	morphine vs. placebo	.013
+8 hours	ketamine vs. morphine	.323
	ketamine vs. placebo	-
	morphine vs. placebo	.323

* significant (Bonferroni correction)
- indicates no comparisons were performed as values were equal

Engage targets with an M16 or M4 series rifle

Fifteen subjects were excluded for incomplete data due to technical malfunction and one subject did not receive one of the test articles due to medical reasons thus resulting in a total of 32 subjects included in the data analysis.

Subjects completed the rifle qualifying task on the EST 2000. To analyze this data, performance in each condition, defined as the mean reaction time to fire, mean aim trace (measured by root mean square error) and mean shot radius (accuracy), was recorded and calculated, in addition to the proportion of hits. The data were analyzed using 6 (target distance: 50m, 100m, 150m, 200m, 250m, 300m) x 3 (drug condition: morphine, placebo, and ketamine) repeated measures ANOVAs. The scores were baseline corrected.

There were no significant main effects of *target distance* or *drug condition* on the dependent variables (reaction time, shot radius, proportion of hits, and aim trace), nor were there interactions as summarized in table 28 and figures 45 - 48. It should be noted that the EST 2000 rifle data was broken out by shooting position (kneeling, prone supported, prone unsupported) for analysis, as well, which did not yield any significant results.

Table 28.
Results of 6 X 3 repeated measures ANOVAs for rifle marksmanship.

Effect term	Dependent Variable	*df*	*F*	*p*	η^2	Observed power
Target Distance						
	Reaction time	2, 62	1.36	0.264	0.042	0.28
	Shot radius	2, 62	0.885	0.418	0.028	0.165
	Prop. of hits	2, 62	1.602	0.210	0.049	0.33
	Aim trace	2, 62	0.361	0.698	0.012	0.11
Drug Condition						
	Reaction time	5,155	1.367	0.24	0.042	0.47
	Shot radius	5,155	1.288	0.272	0.04	0.26
	Prop. of hits	5,155	0.474	0.795	0.015	0.18
	Aim trace	5,155	0.476	0.793	0.015	0.18
Interaction						
	Reaction time	10, 310	1.119	0.348	0.59	0.28
	Shot radius	10, 310	0.218	0.995	0.007	0.09
	Prop. of hits	10, 310	1.083	0.374	0.034	0.57
	Aim trace	10, 310	1.003	0.441	0.031	0.53

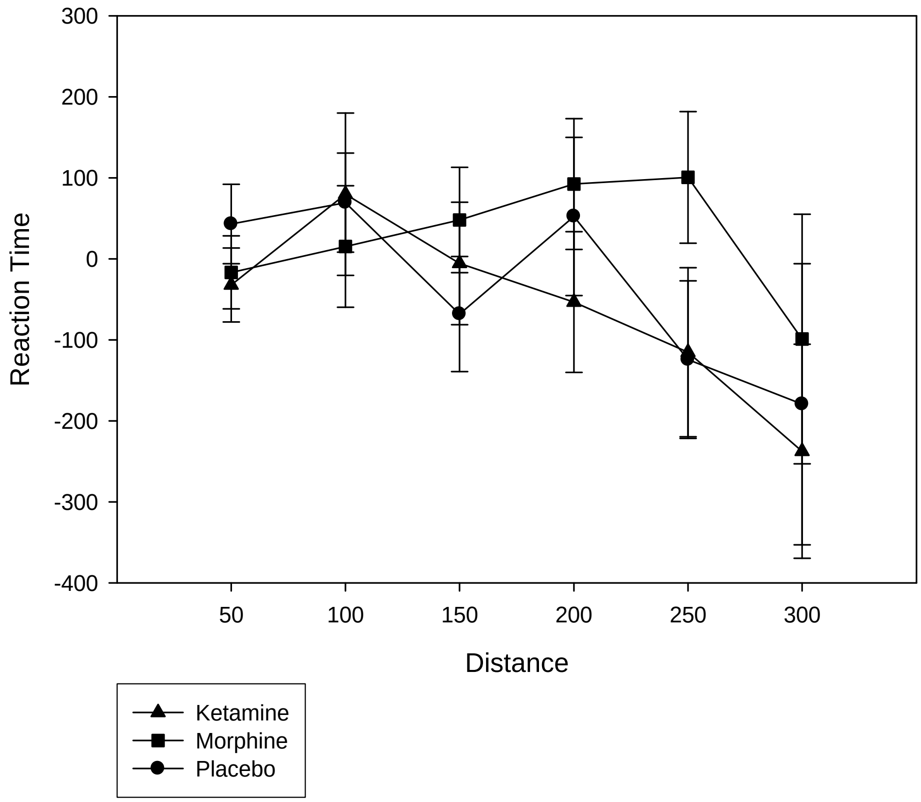


Figure 45. EST 2000 (rifle): Mean reaction time (milliseconds) by condition (ketamine, morphine, placebo) and distance (meters).

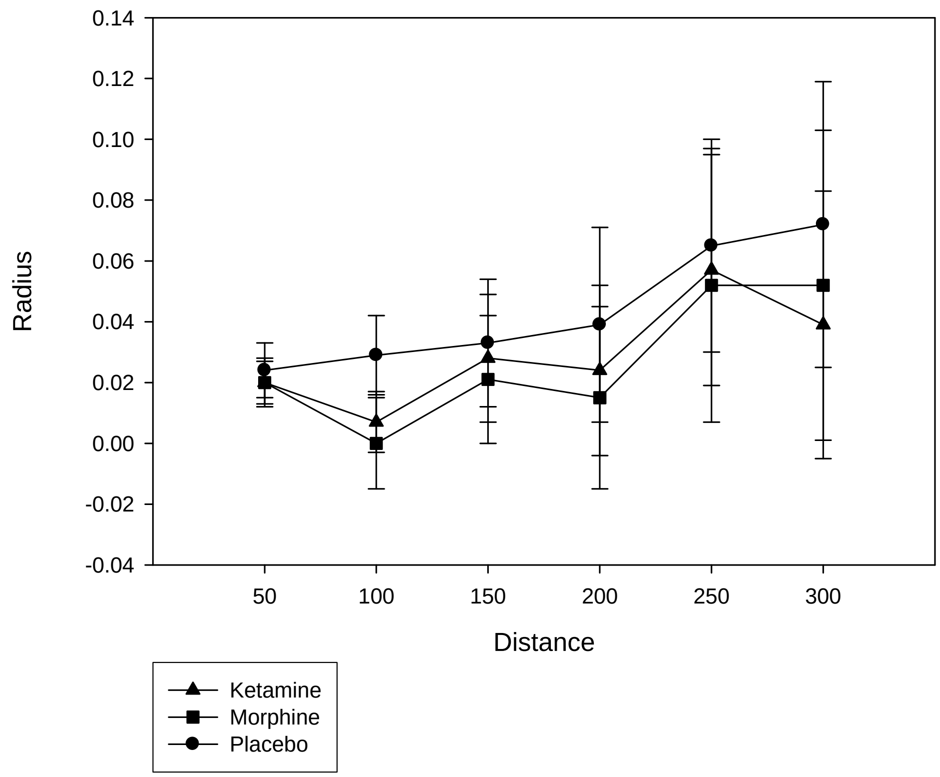


Figure 46. EST 2000 (rifle): Mean shot radius (meters) by condition (ketamine, morphine, placebo) and distance (meters).

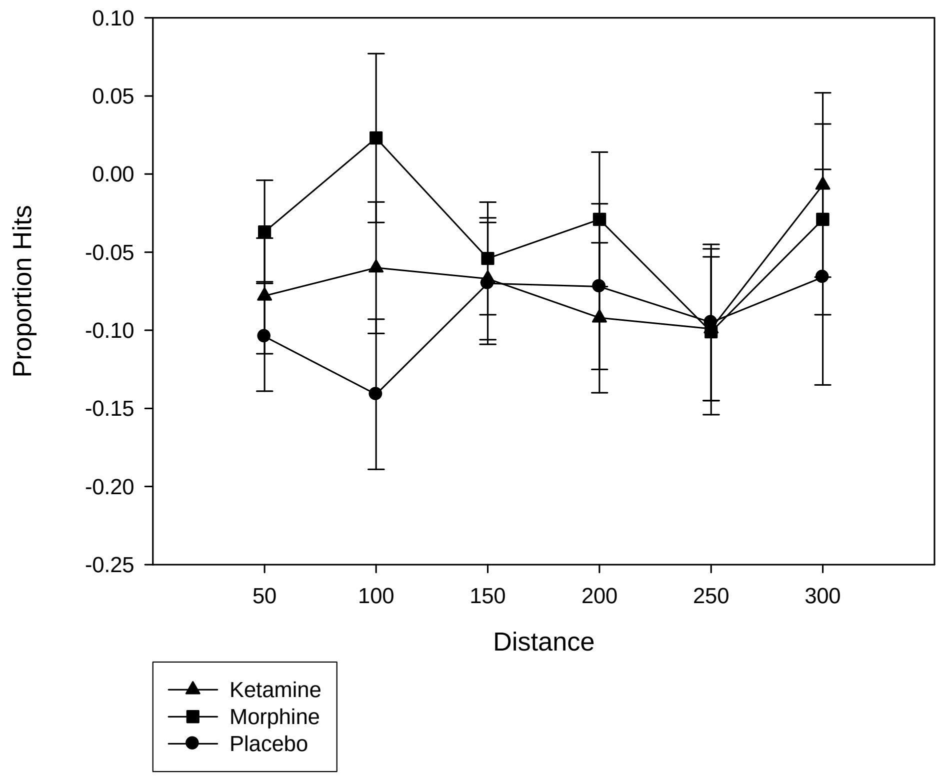


Figure 47. EST 2000 (rifle): Mean proportion of hits by condition (ketamine, morphine, placebo) and distance (meters).

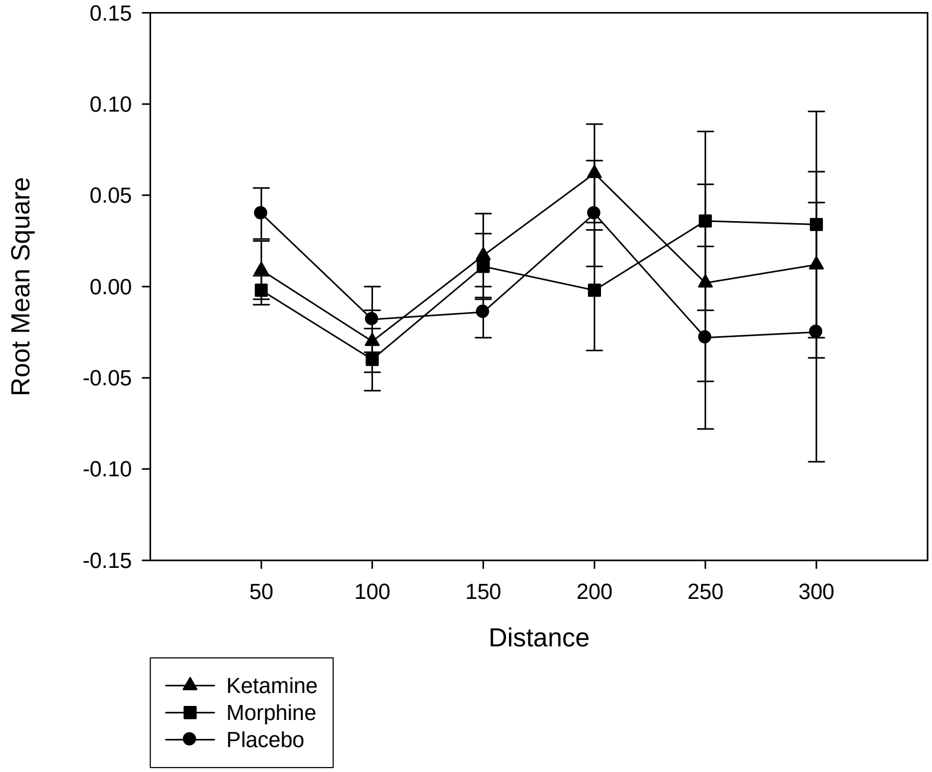


Figure 48. EST 2000 (rifle): Mean aim trace (root mean square, meters) by condition (ketamine, morphine, placebo) and distance (meters).

Correct malfunctions of an M16 or M4 series rifle

Correct rifle malfunction is commonly referred to as SPORTS, the acronym for the subtasks of slap upward on the magazine to ensure its seated, pull the charging handle back, observe the ejection of the cartridge and check for obstructions, release the charging handle to feed another round into the chamber, tap the forward assist, and squeeze the trigger. The Soldier's Manual of Common Tasks imposes no time requirements on this task to pass (only that steps are completed properly), but time was recorded for purposes of this study.

A total of 46 participants were included for analysis. Performance was baseline corrected. A Chi-square test was conducted on the accuracy of the SPORTS task with three conditions (ketamine, morphine, and placebo). Drug condition was not significant, $\chi^2(2, N = 46) = 3.917$, $p = 0.141$. Results are depicted in figure 49.

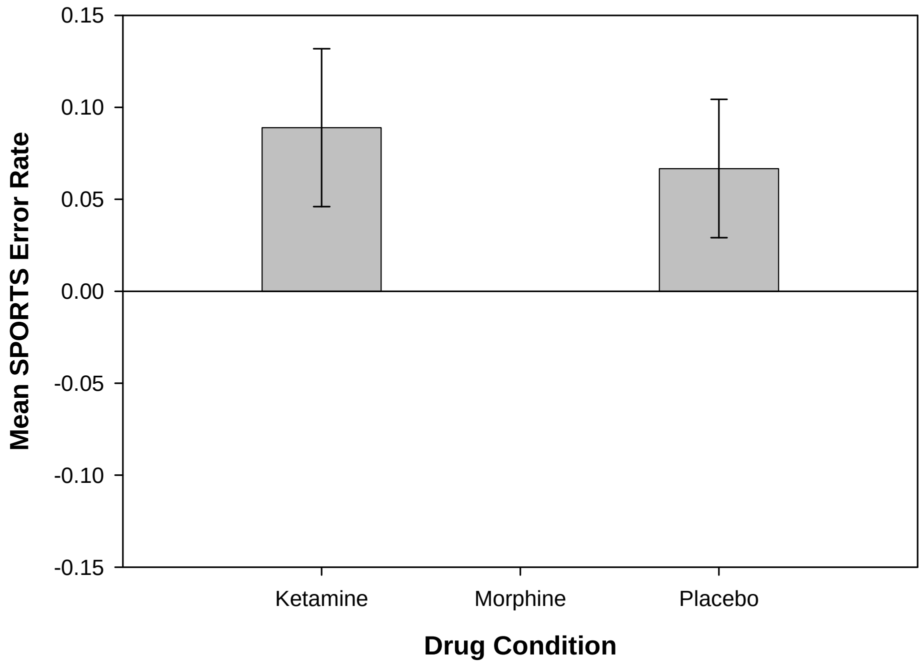


Figure 49. SPORTS mean error rate by drug condition.

A within subjects ANOVA was conducted on the performance times of the SPORTS task with three conditions (ketamine, morphine, and placebo). Drug condition was not significant, $F(2, 90) = 0.710$, $p = 0.495$, observed power = 0.167. Results are depicted in figure 50.

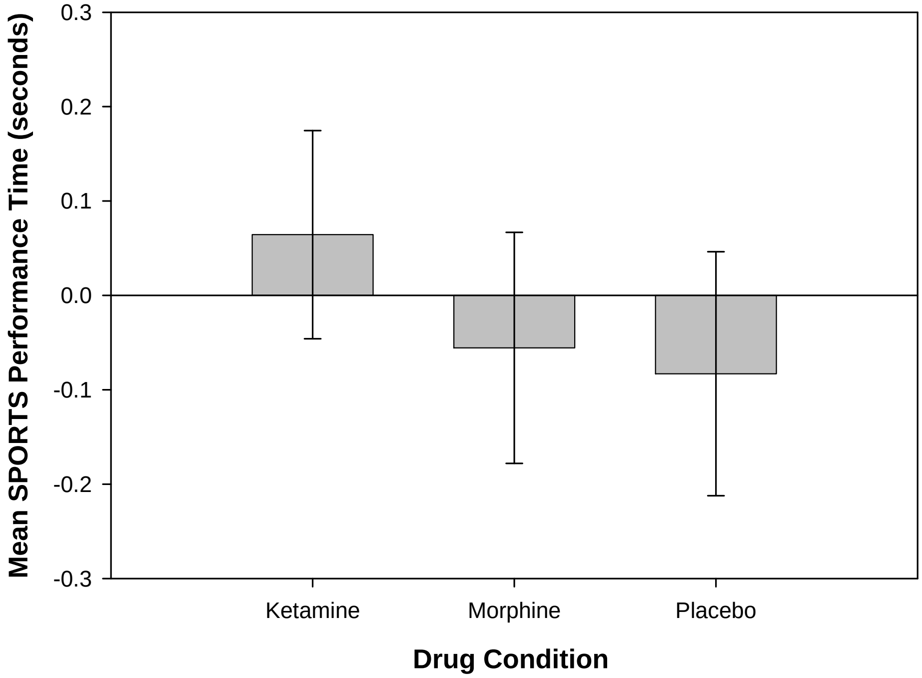


Figure 50. SPORTS mean performance times by drug condition.

Shoot—Don't shoot (Identify targets)

Fifteen subjects were excluded for incomplete data due to technical malfunction and one subject did not receive one of the test articles due to medical reasons thus resulting in a total of 32 subjects included in the data analysis.

Using the 9-mm, subjects completed a friend/foe detection task. In order to analyze performance in each condition, for each correctly identified enemy target, including the reaction time to fire, aim trace (measured by root mean square error) and shot radius (accuracy) was recorded and calculated, in addition to the proportion of hits. The data were analyzed using repeated measures ANOVAs. The independent variable, *drug condition*, was the within-subjects factor and its three levels were morphine, placebo, and ketamine. The scores were baseline corrected. For the shot radius data, the assumption of sphericity was violated and a Greenhouse-Geisser correction was used. There were no significant main effects of *drug condition* on any of the four dependent measures: reaction time, $F(2, 62) = 0.495$, $p = 0.612$, $\eta^2 = 0.042$, observed power = 0.28; shot radius, $F(1.674, 51.883) = 0.757$, $p = 0.452$, $\eta^2 = 0.028$, observed power = 0.16; proportion of hits, $F(2, 62) = 0.103$, $p = 0.902$, $\eta^2 = 0.05$, observed power = 0.32; aim trace, $F(2, 62) = 0.806$, $p = 0.451$, $\eta^2 = 0.012$, observed power = 0.10; figures 51 - 54.

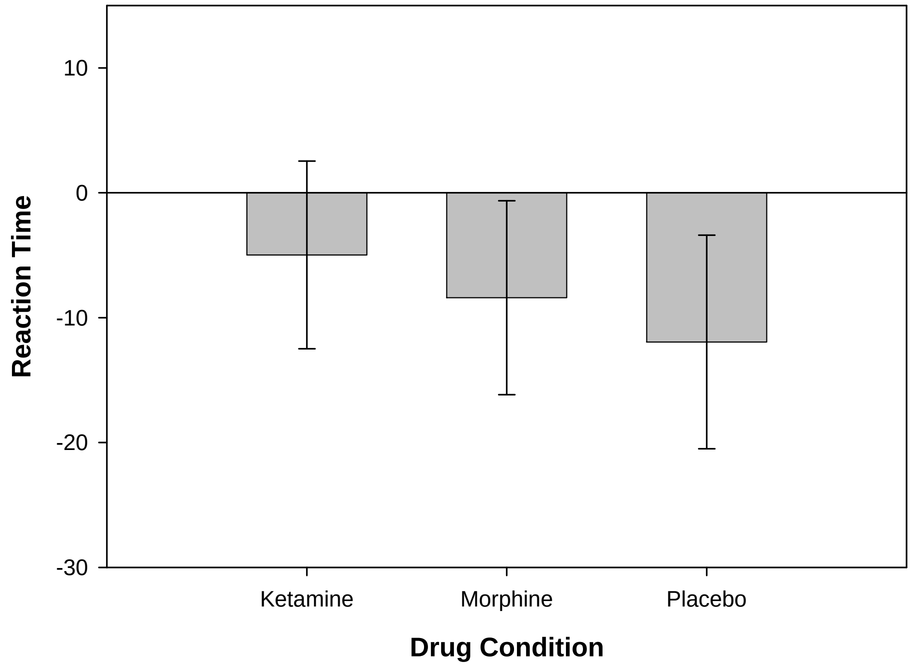


Figure 51. EST 2000 (9-mm): Mean reaction time by drug condition.

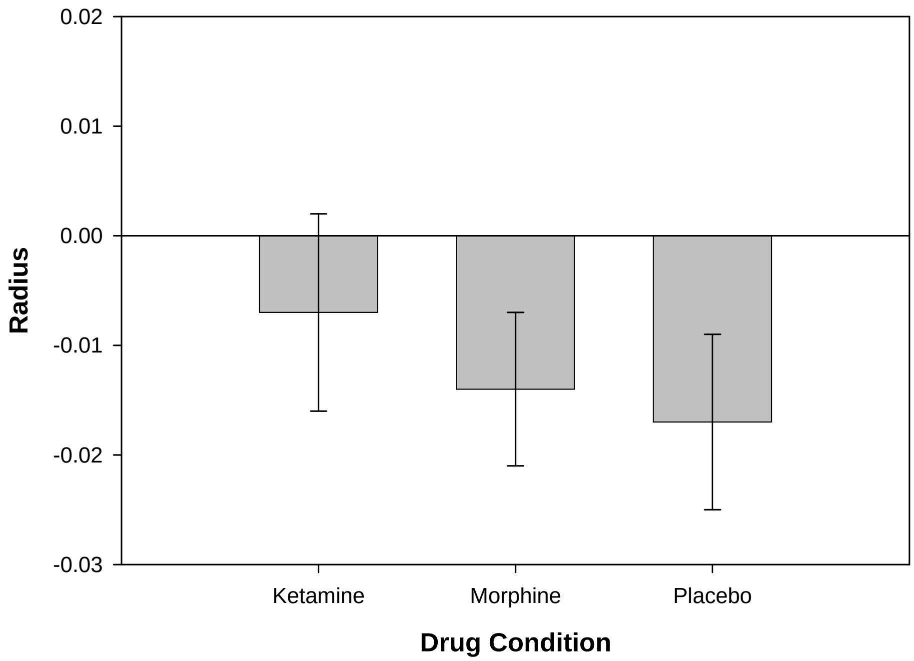


Figure 52. EST 2000 (9-mm): Mean shot radius by drug condition.

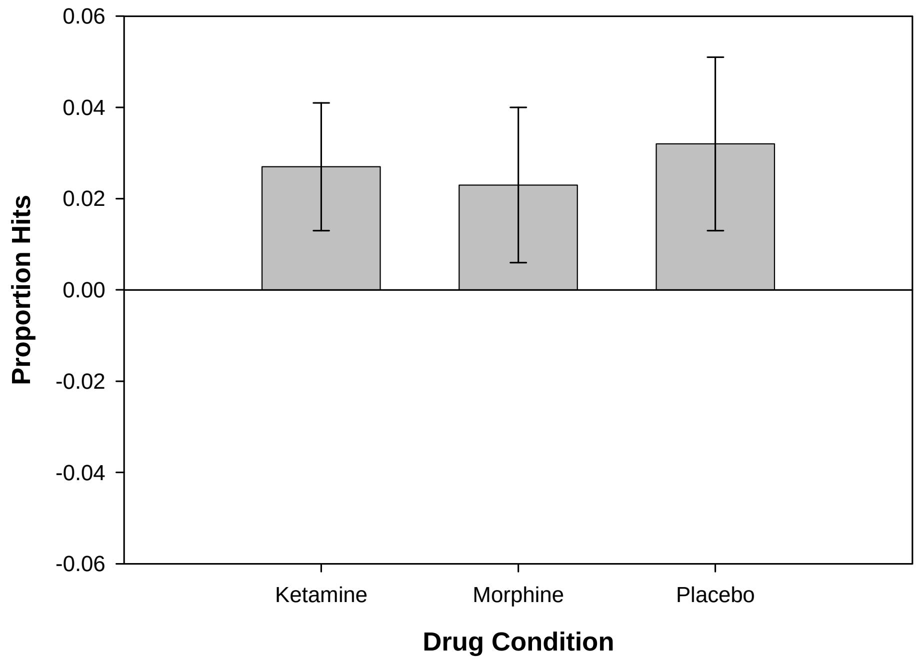


Figure 53. EST 2000 (9-mm): Mean proportion of hits by drug condition.

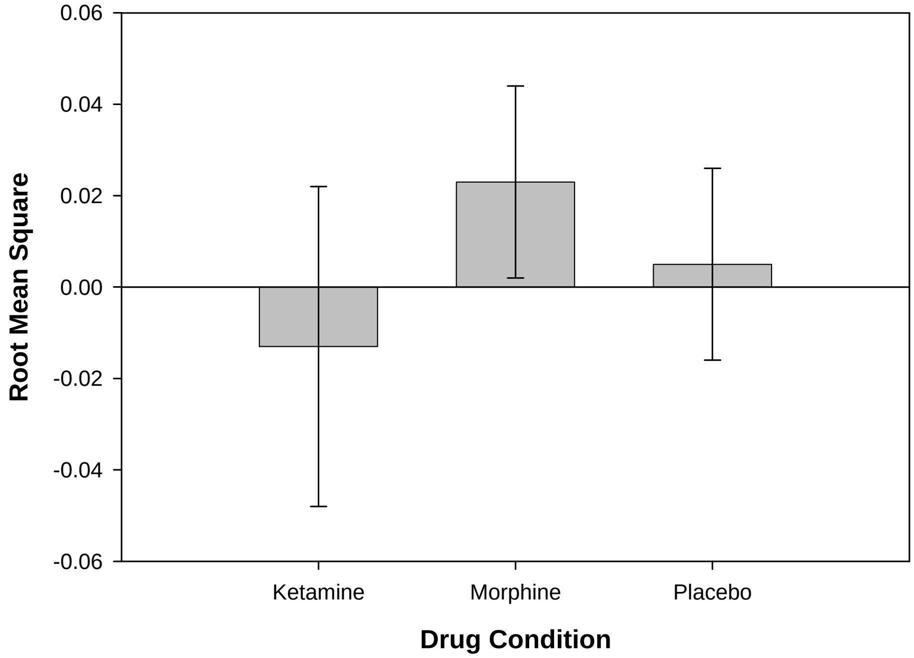


Figure 54. EST 2000 (9-mm): Mean aim trace (root mean square) by drug condition.

Mission-Oriented Protective Posture (MOPP) gear and protective mask

Don protective mask

Protection of self using the mask was divided into two tasks. The first task entailed donning, clearing, and checking the protective mask (ProMask) within nine seconds. The second task entailed securing the hood. Forty-six participants were included in the analysis. Performance was baseline corrected.

Independent Chi-square tests were conducted on the accuracy of the ProMask for each of the two tasks; each test contained three drug conditions (ketamine, morphine, and placebo). Drug condition was not significant for ProMask task 1, $\chi^2(4, N = 46) = 5.476$, $p = 0.242$ or task 2, $\chi^2(2, N = 46) = 3.604$, $p = 0.165$. Mean error rates for ProMask tasks 1 and 2 are presented in figures 55 and 56, respectively.

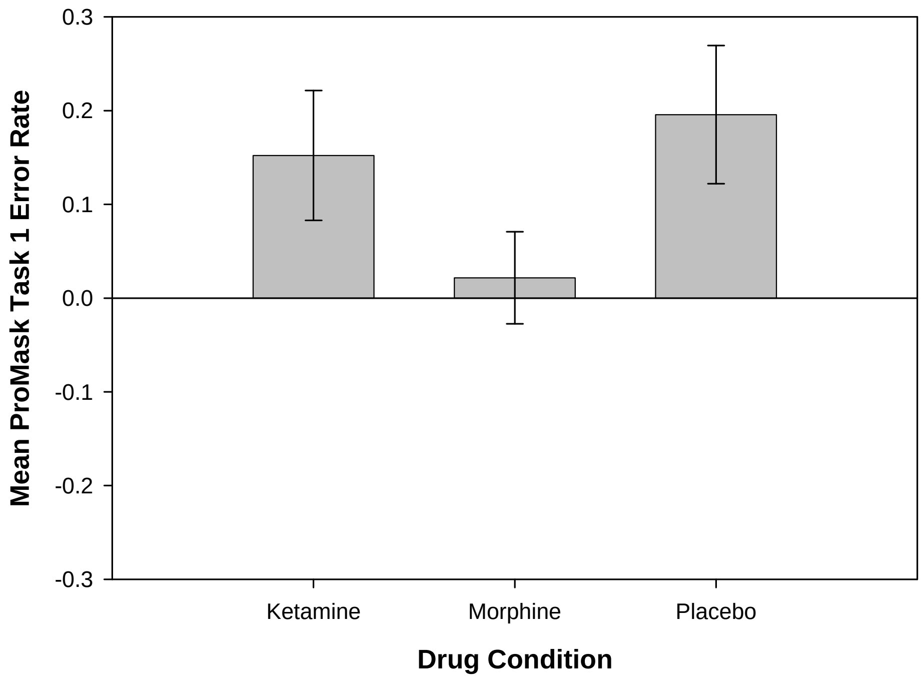


Figure 55. ProMask task 1 mean error rates.

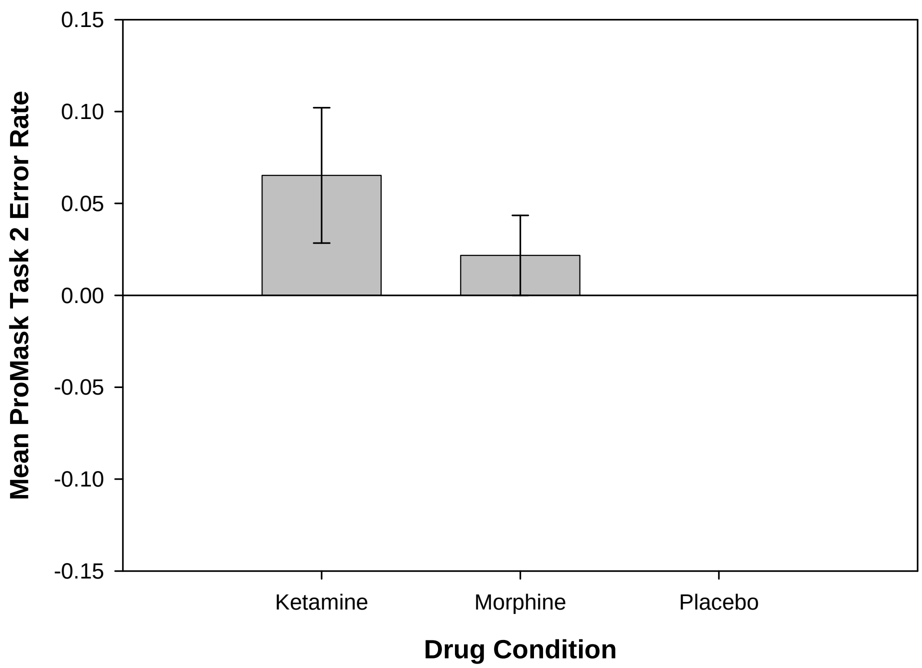


Figure 56. ProMask task 2 mean error rates.

Two independent, within subjects ANOVAs were conducted on the performance times of the ProMask task for each separate part of the task. Each test contained three drug conditions

(ketamine, morphine, and placebo). There was a significant difference for ProMask task 1, *F* (2, 69.911) = 4.004, $p = 0.032$, (Greenhouse-Geisser corrected) observed power = 0.632; but not for ProMask task 2, $F(2, 90) = 1.142$, $p = 0.324$, observed power = 0.246. Mean performance times for ProMask tasks 1 and 2 are depicted in figures 57 and 58, respectively. Post-hoc Bonferroni corrected pairwise comparisons ($\alpha = .05/3 = .017$) were conducted on the results for the ProMask task 1 (table 29) with significant differences between ketamine and morphine conditions (p = 0.002).

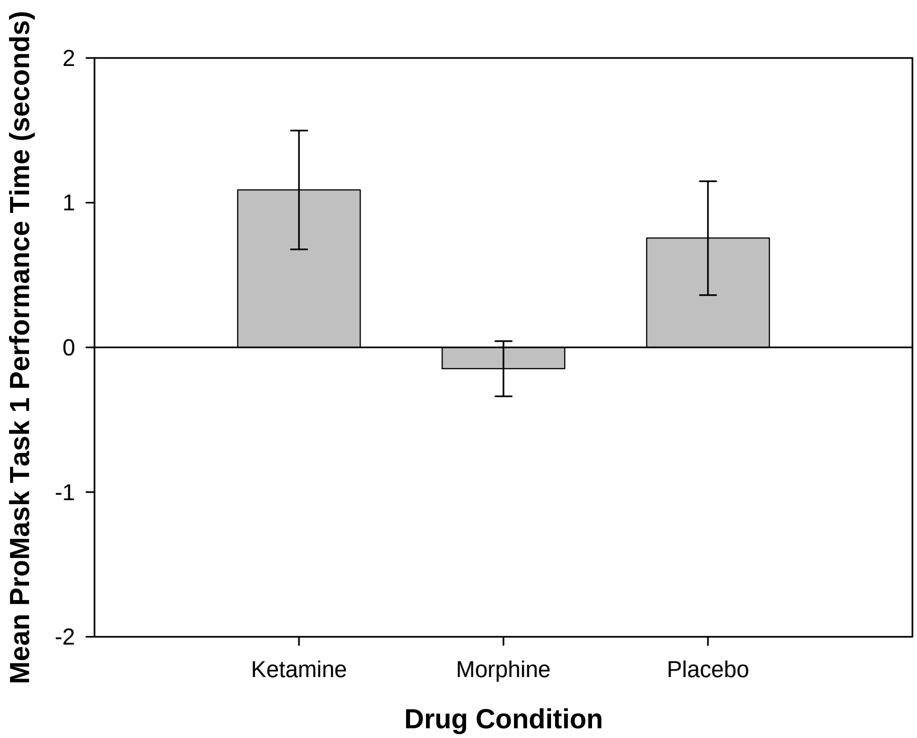


Figure 57. ProMask task 1 mean performance times.

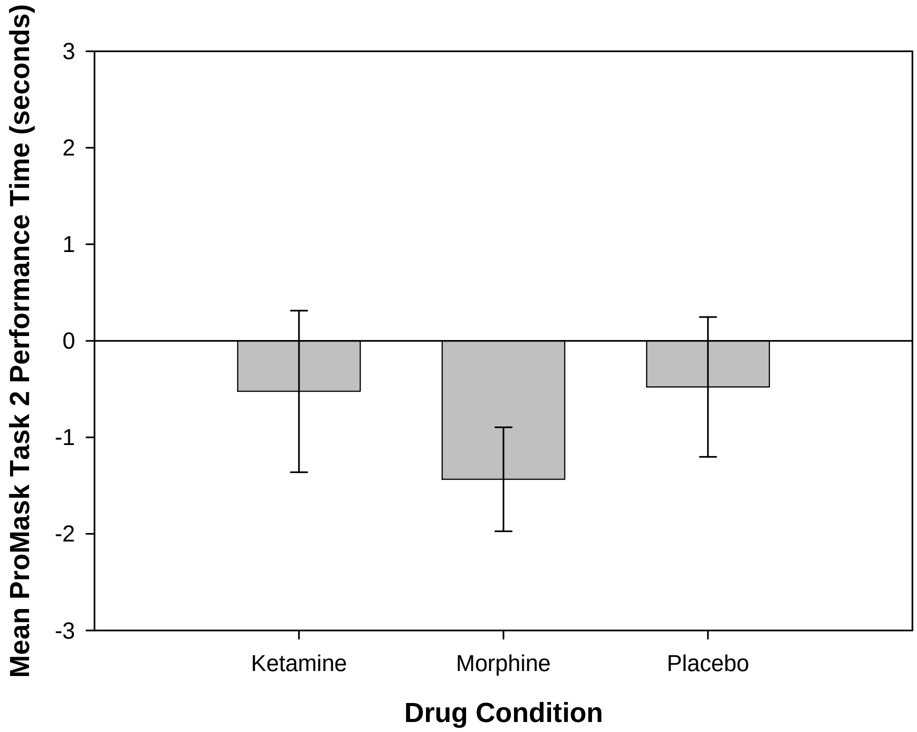


Figure 58. ProMask task 2 mean performance times.

Table 29.
Post hoc results for drug effect for ProMask Tasks.

Task/Measurement	Comparison	*p*
Performance Time	ketamine vs. morphine	0.002*
Task 1	ketamine vs. placebo	0.397
	morphine vs. placebo	0.023

* significant (Bonferroni correction)

Mission-Oriented Protective Posture (MOPP)

MOPP tasks were divided into four subtasks in accordance with each of the MOPP levels (1 = don trousers and jacket; 2 = don overboots, 3 = don protective mask, and 4 = don protective gloves) within eight minutes or less. 46 participants were included in the analysis. Performance was baseline corrected.

Four independent Chi-square tests were conducted on the accuracy of the MOPP tasks; each test contained three drug conditions (ketamine, morphine, and placebo). Drug condition did not result in significant differences for any of the MOPP tasks: $\chi^2(4, N = 46) = 0.576$, $p = 0.966$, $\chi^2(2, N = 46) = 2.905$, $p = 0.234$, $\chi^2(2, N = 46) = 1.730$, $p = 0.421$ and $\chi^2(2, N = 46) = 3.136$, $p = 0.365$

for tasks 1 through 4, respectively. Mean error rates for the MOPP 1, 2, 3 and 4 are presented in figures 59, 60, 61, and 62, respectively.

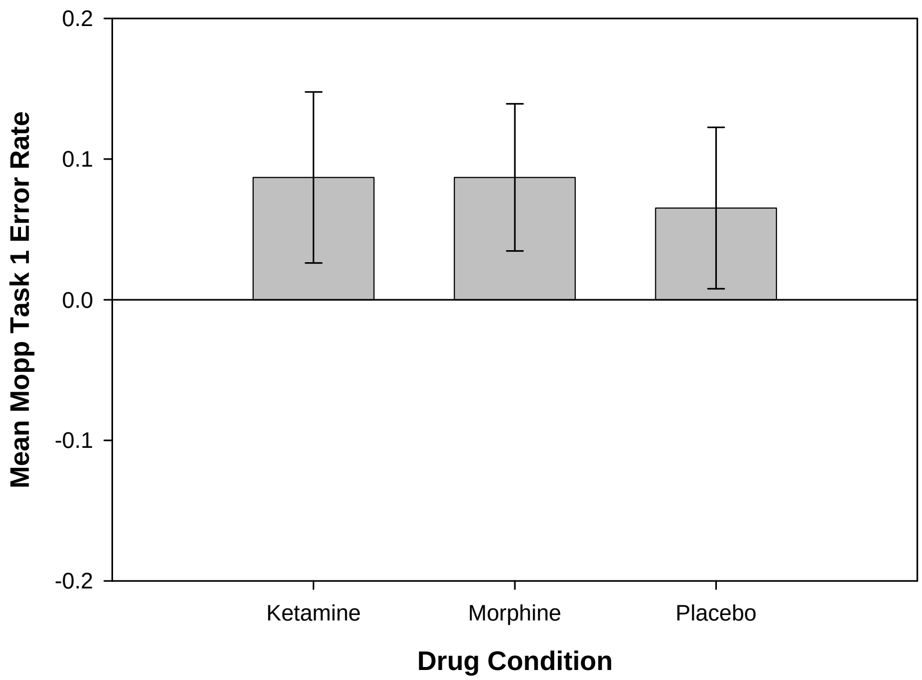


Figure 59. MOPP task 1 mean error rates.

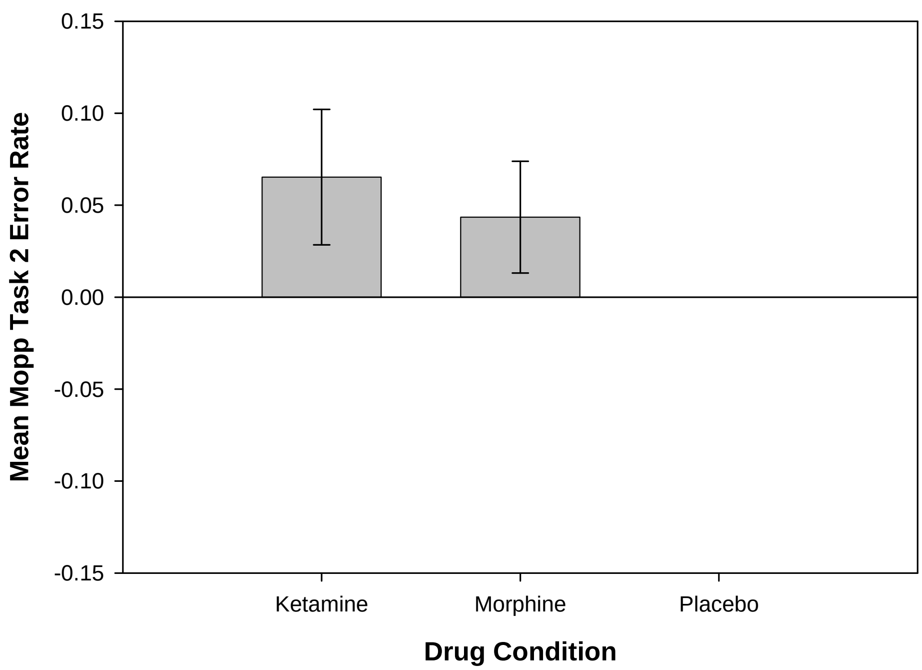


Figure 60. MOPP task 2 mean error rates.

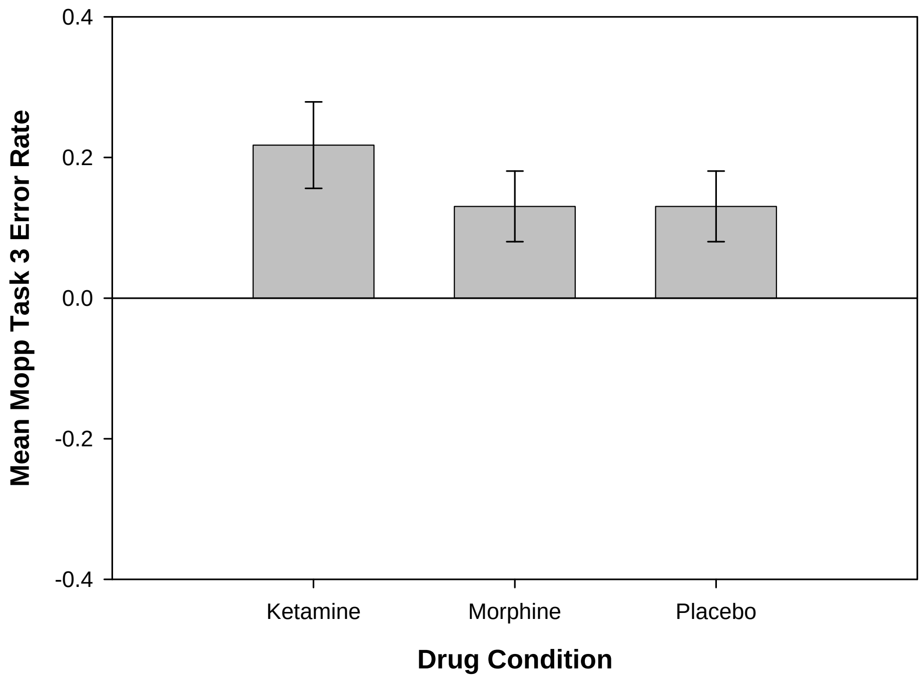


Figure 61. MOPP task 3 mean error rates.

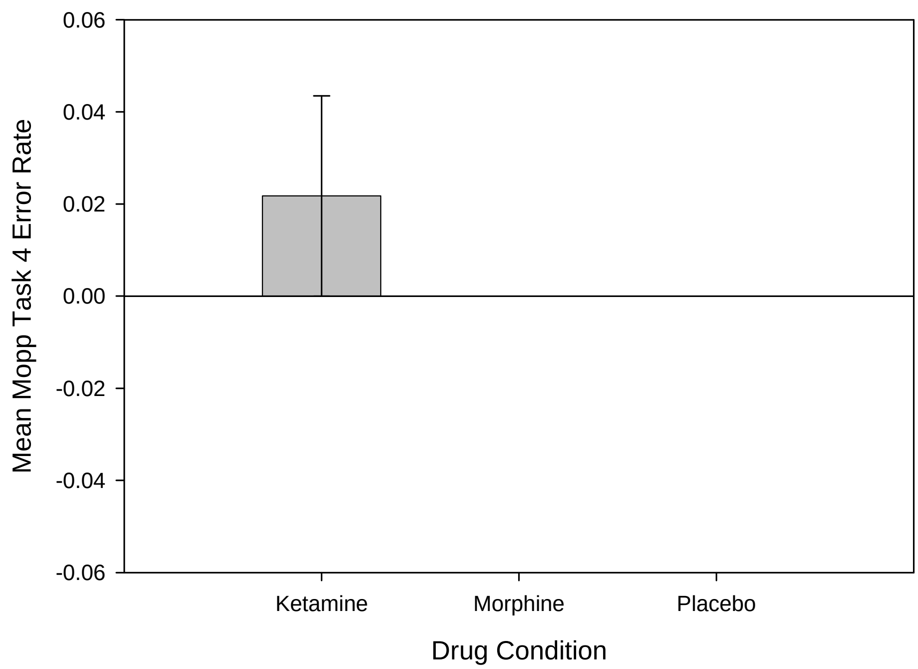


Figure 62. MOPP task 4 mean error rates.

Four independent, within subjects ANOVAs were conducted on the performance times of the MOPP tasks; each test contained three drug conditions (ketamine, morphine, and placebo).

There were significant differences for MOPP task 1, F (2, 90) = 15.715, $p < 0.001$, observed power = 0.999; task 2, F (2, 90) = 14.771, $p < 0.001$, observed power = 0.999; task 3, F (2, 90) = 13.545, $p < 0.001$, observed power = 0.998; and task 4, F (2, 90) = 17.301, $p < 0.001$, observed power = 1.000. Mean performance times for the MOPP 1, 2, 3 and 4 tasks are depicted in figures 63, 64, 65, and 66, respectively. Post-hoc Bonferroni corrected pairwise comparisons (α = .05/3 = .017) were conducted on the results of each MOPP task (table 30) and found ketamine to be significantly different from both morphine and placebo in all four parts of the task (all significance were p = 0.001 or less).

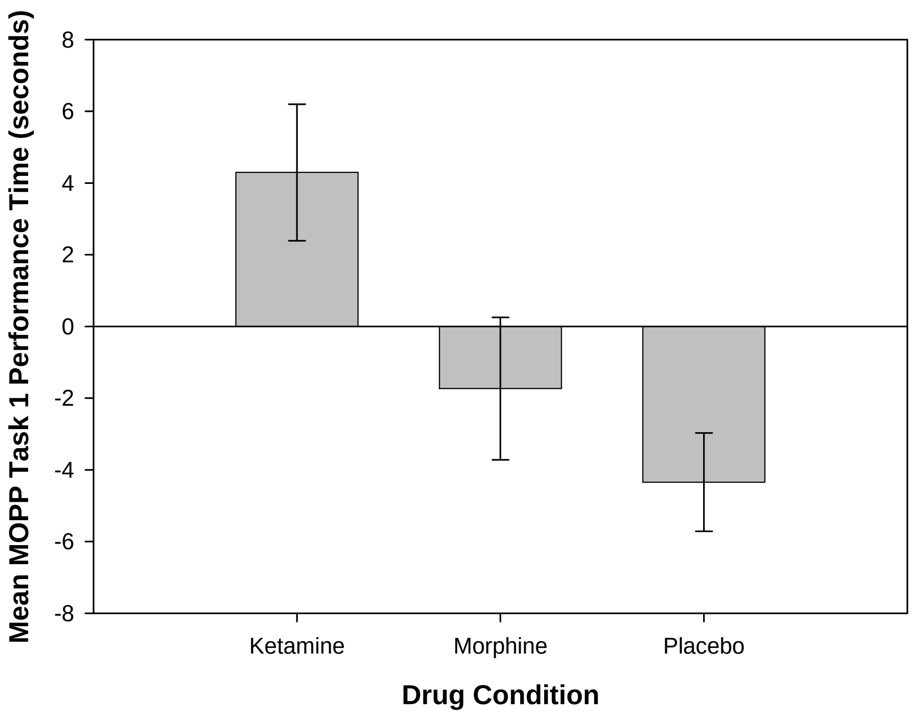


Figure 63. MOPP task 1 mean performance times.

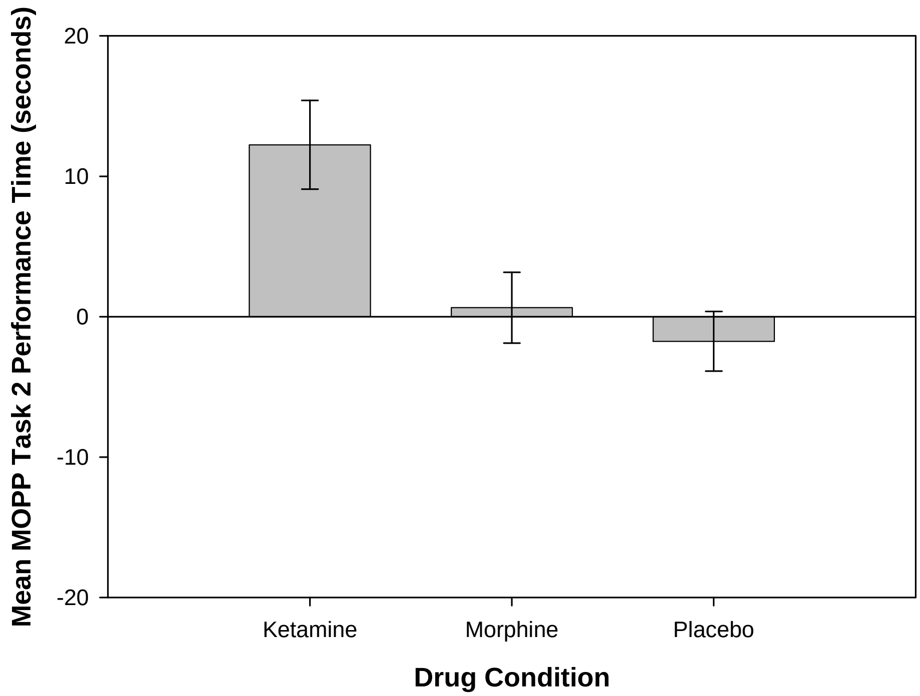


Figure 64. MOPP task 2 mean performance times.

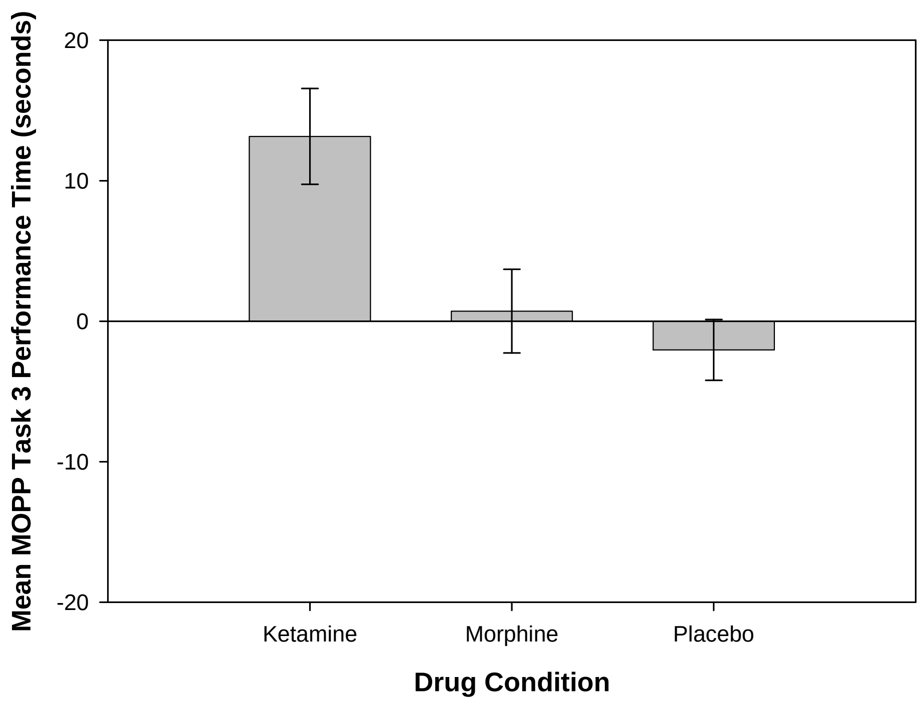


Figure 65. MOPP task 3 mean performance times.

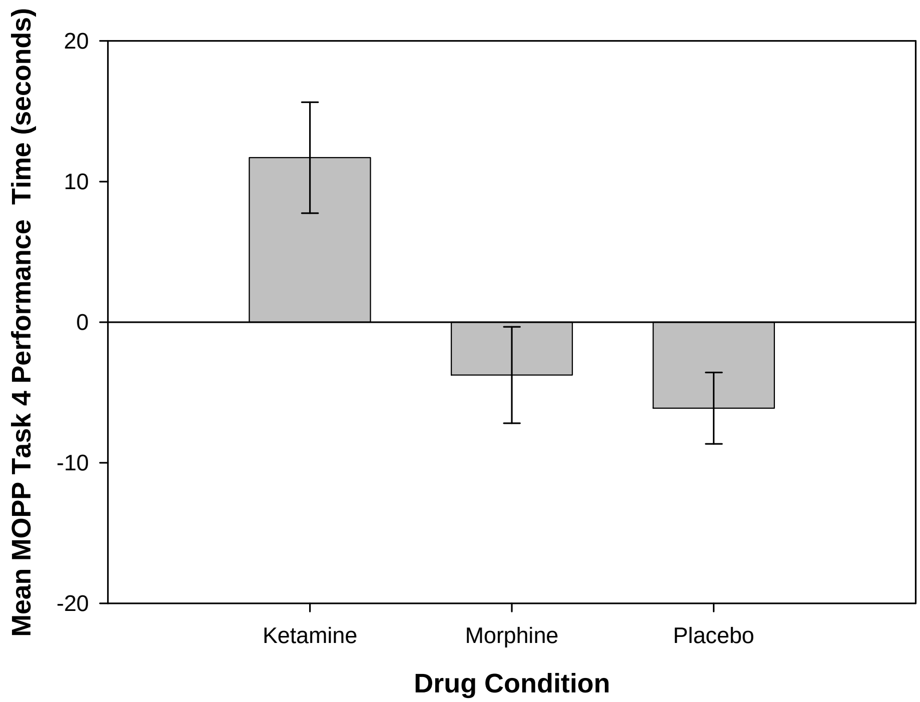


Figure 66. MOPP task 4 mean performance times.

Table 30.
Post hoc results for drug effect for MOPP Tasks.

Task/Measurement	Comparison	*p*
Performance Time Task 1	ketamine vs. morphine	0.001*
	ketamine vs. placebo	<0.001*
	morphine vs. placebo	0.063
Performance Time Task 2	ketamine vs. morphine	<0.001*
	ketamine vs. placebo	<0.001*
	morphine vs. placebo	0.366
Performance Time Task 3	ketamine vs. morphine	0.001*
	ketamine vs. placebo	<0.001*
	morphine vs. placebo	0.365
Performance Time Task 4	ketamine vs. morphine	<0.001*
	ketamine vs. placebo	<0.001*
	morphine vs. placebo	0.450

* significant (Bonferroni correction)

Perform voice communications and request medical evacuation

Perform voice communications/radio task

Subjects were presented with disassembled parts of an AN/PRC-90 handheld radio and tested on speed and accuracy of bringing the radio to mechanical functionality and entering the radio net using correct call signs, sequence, prowords, and phonetic alphabet and numerals. Performance was baseline corrected.

A Chi-square test was conducted on the accuracy of the radio task with three drug conditions (ketamine, morphine, and placebo). Drug conditions did not result in significant differences for the task, $\chi^2(2, N = 46) = 3.136$, $p = 0.208$. Mean error rates are presented in figure 67.

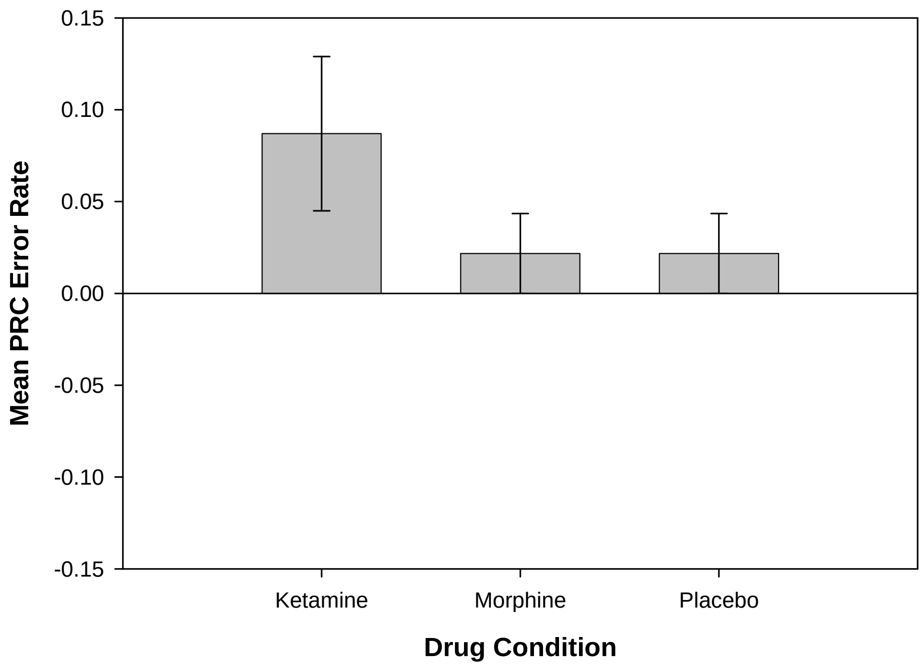


Figure 67. Voice communications/radio task mean error rates.

A within subjects ANOVA was conducted on the performance times of the voice communications task with three drug conditions (ketamine, morphine, and placebo). Drug conditions did not result in significant differences, $F(2, 77.162) = 1.984$, $p = 0.151$, (Greenhouse-Geisser corrected) observed power = 0.369. Mean performance times are depicted in figure 68.

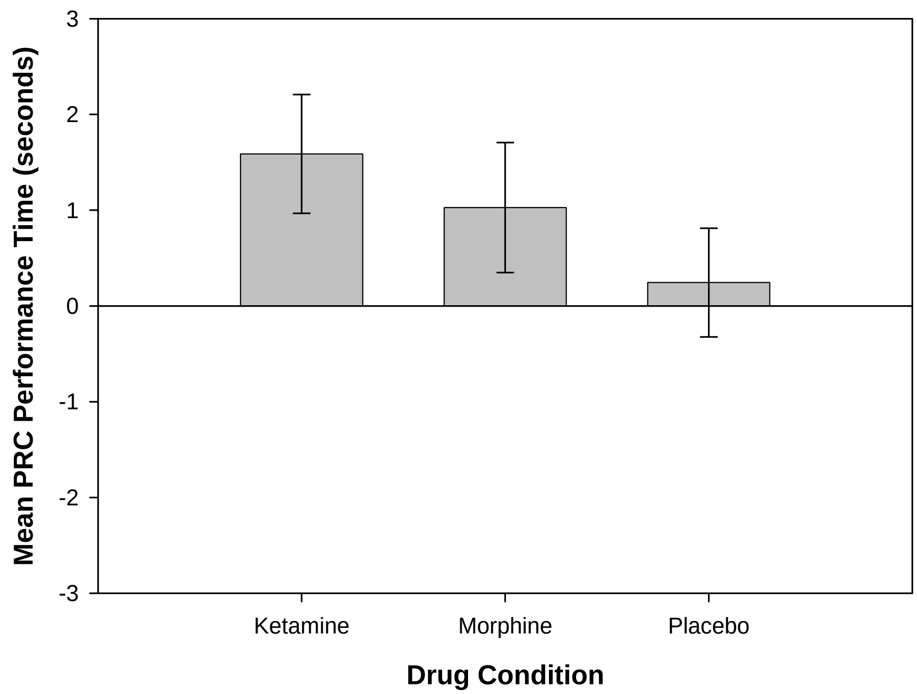


Figure 68. Voice communications/radio task mean performance times.

Request medical evacuation

Subjects were required to interpret a multiple casualty scenario, extract pertinent information, and transmit a standard 9-line MEDEVAC request providing all necessary information and using all proper brevity codes. The 9-line was separated into two tasks: task 1 consisted of MEDEVAC lines 1-5 (must be completed within first 25 seconds of radio transmission) and task 2 consisted of lines 6-9 (no time limit for completion). Performance was baseline corrected.

Two independent Chi-square tests were conducted on the accuracy of the 9-line MEDEVAC corresponding to the two tasks; each test contained three drug conditions (ketamine, morphine, and placebo). Drug conditions did not result in a significant difference for task 1, $\chi^2(2, N = 46) = 0.515$, $p = 0.773$); but did yield significance for the 9-line task 2, $\chi^2 (4, N = 46) = 11.016$, $p = 0.026$. Mean error rates for tasks 1 and 2 are presented in figures 69 and 70, respectively. Post-hoc Bonferroni corrected pairwise comparisons ($\alpha = .05/3 = .017$) were conducted for 9-line task 2 and found that morphine and placebo conditions approached significance (p = 0.018), but that no conditions were significantly different.

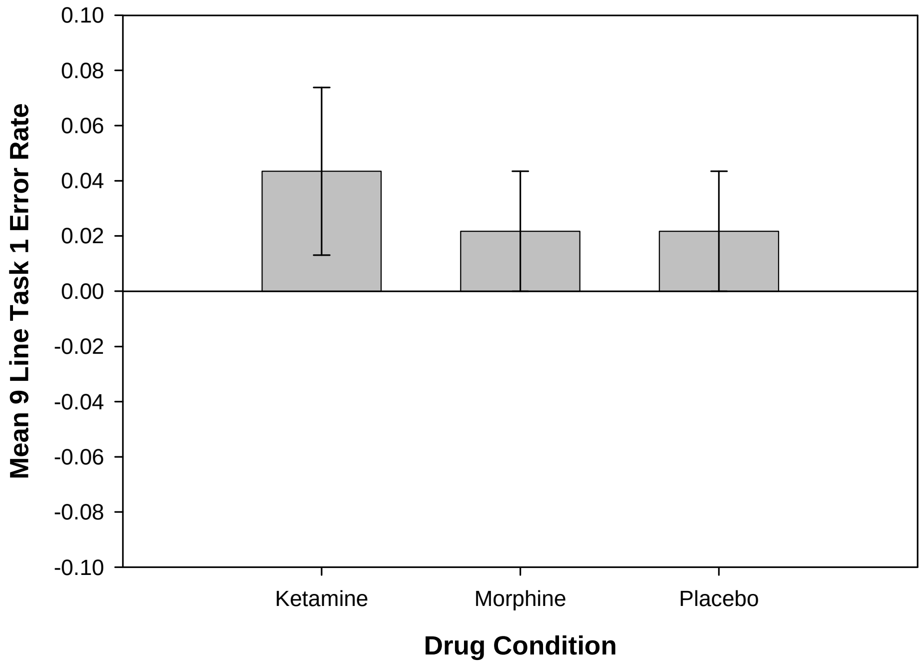


Figure 69. 9-line task 1 mean error rates.

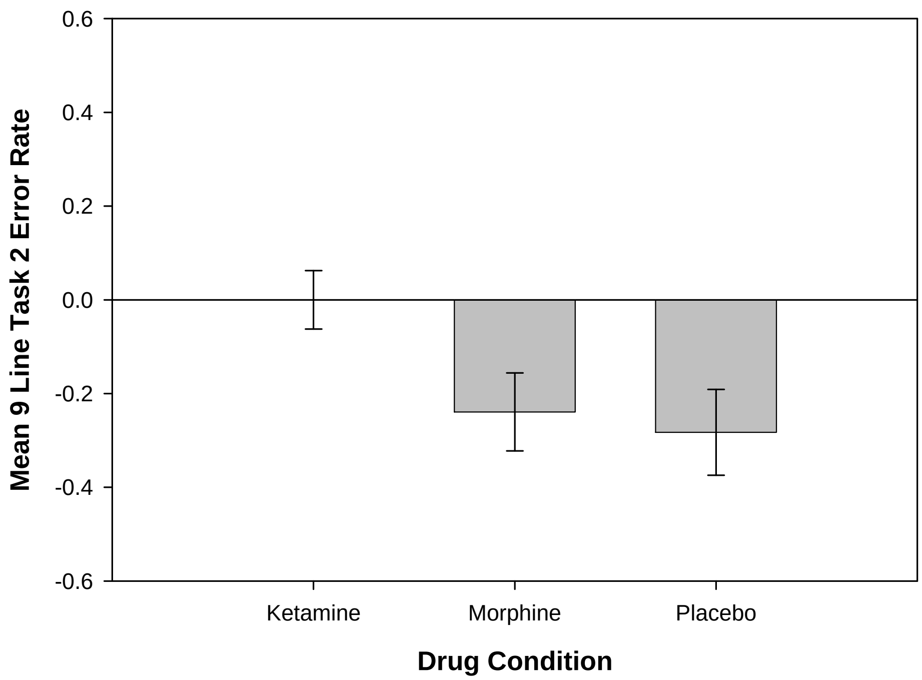


Figure 70. 9-line task 2 mean error rates.

The 9-line task consisted of multiple steps required to be conducted properly in order to pass the task. The accuracy analysis described above only accounts for a scoring of “pass or fail.” Additional descriptive analysis was conducted to present the number of errors made per drug session when errors were made (depicted in figure 71).

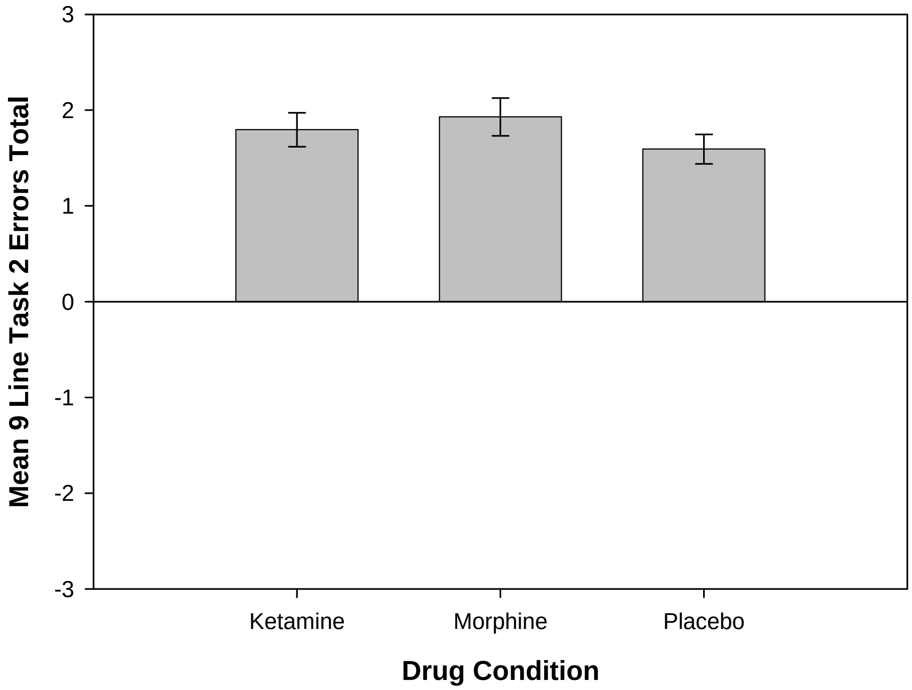


Figure 71. 9-line total errors (when errors were made).

Two independent, within subjects ANOVAs were conducted on the performance times of the 9-line corresponding with the two separate parts of the task; each test contained three drug conditions (ketamine, morphine, and placebo). Drug condition did not result in significant differences for the 9-line task 1, $F(2, 88) = 3.189$, $p = 0.676$, observed power = 0.112; but significant differences did exist for task 2, $F\ (2, 88) = 5.368$, $p = 0.006$, observed power = 0.830. Mean response times for 9-line tasks 1 and 2 are depicted in figures 72 and 73, respectively. Post-hoc Bonferroni corrected pairwise comparisons ($\alpha = .05/3 = .017$) were conducted on the results for task 2 results (table 31) with significant differences between ketamine and both morphine and placebo conditions ($p = 0.006$ and $p = 0.012$, respectively).

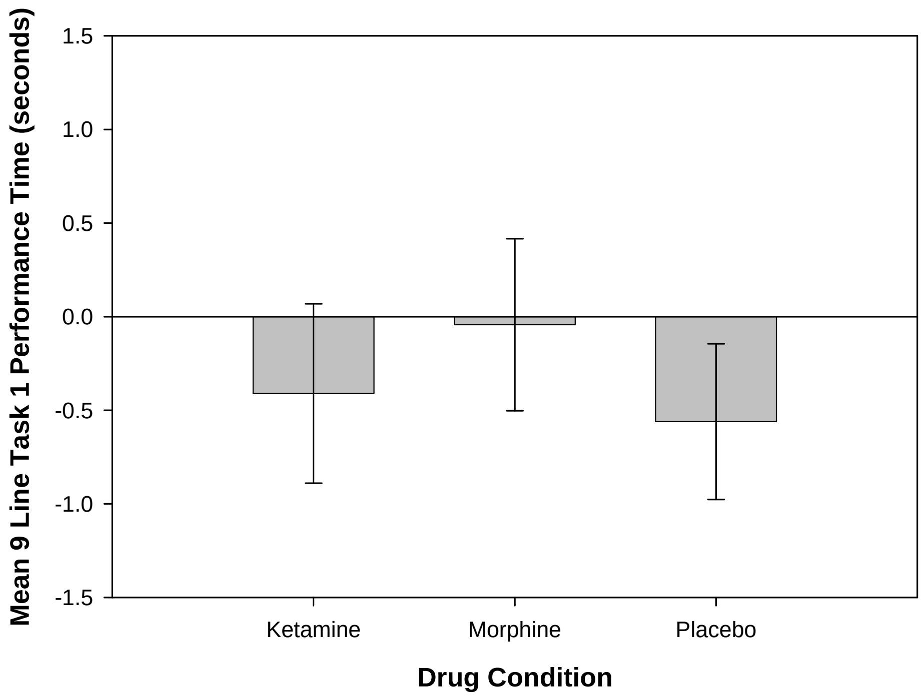


Figure 72. 9-line task 1 mean performance times.

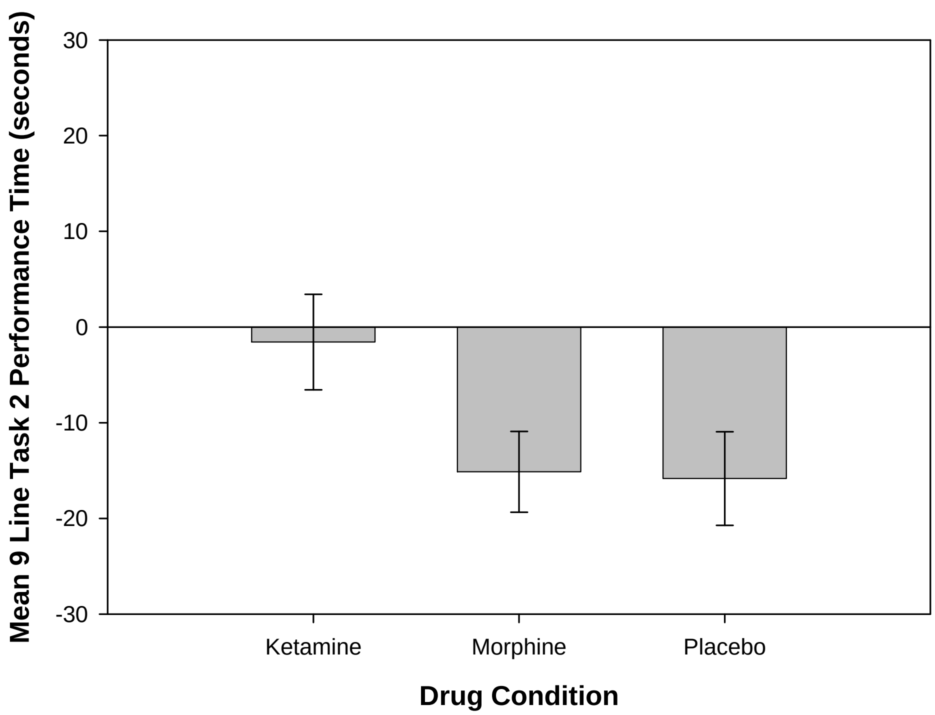


Figure 73. 9-line task 2 mean performance times.

Table 31.
Post hoc results for drug effect for MEDEVAC Tasks.

Task/Measurement	Comparison	*p*
Accuracy	ketamine vs. morphine	0.097
Task 2	ketamine vs. placebo	0.687
	morphine vs. placebo	0.018
Performance Time	ketamine vs. morphine	0.006*
Task 2	ketamine vs. placebo	0.012*
	morphine vs. placebo	0.943

* significant (Bonferroni correction)

Evaluation of Risks (EVAR) questionnaire

To evaluate the results of the EVAR, the total and three sub-scale (*risk/thrill-seeking*, *need-for-control*, and *self-confidence*) scores were calculated for each *drug condition* (baseline, morphine, placebo, and ketamine). The scores were then baseline adjusted by subtracting one's baseline score from each other condition resulting in three levels of the independent variable, *drug condition*; baseline-adjusted morphine, baseline-adjusted placebo, and baseline-adjusted ketamine. The data were analyzed using a repeated measures multivariate analysis of variance (MANOVA). For all three dependent measures, the assumption of sphericity was violated and a Greenhouse-Geisser correction was used. Four subjects were excluded from the analysis for incomplete data resulting from failure to respond to all questions in the assessment, and one subject did not receive one of the test articles due to medical reasons. Forty-three subjects were included in the analysis.

For the *risk/thrill-seeking* sub-scale scores, there was a significant effect of *drug condition*, $F(2.15, 90.36) = 11.60$, $p < .001$, $\eta^2 = 0.22$, observed power = 0.99 (figure 74). Paired comparison *t*-tests revealed that subjects showed a significantly greater change from baseline in the ketamine condition than in the morphine or placebo conditions. In the morphine condition, subjects showed a negative change in scores contrary to the positive change in the placebo condition. The results of the paired comparisons are summarized in table 32.

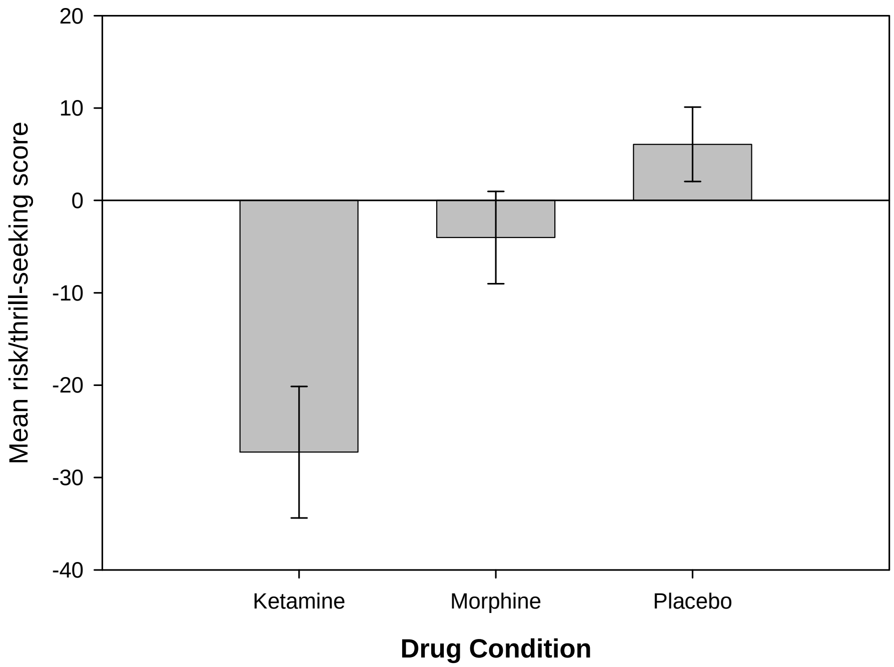


Figure 74. Mean risk/thrill-seeking score by condition.

Table 32.
Results of paired comparison *t*-tests for risk/thrill-seeking sub-scale scores (baseline adjusted).

Comparison	*p*
morphine vs. placebo	033*
morphine vs. ketamine	.003*
placebo vs. ketamine	.001*

* significant

There was a significant effect of *drug condition* on *self-confidence* scores, $F(2.11, 88.65) = 10.64$, $p = .001$, $\eta^2 = 0.20$, observed power = 0.99 (figure 75). Subsequent paired comparison *t*-tests showed that in the ketamine condition, subjects' confidence decreased from baseline significantly more (thus a larger difference in scores) than in the morphine and placebo conditions (table 33). Also, in the morphine condition, baseline-adjusted scores decreased more than in the placebo condition; a difference which approached significance.

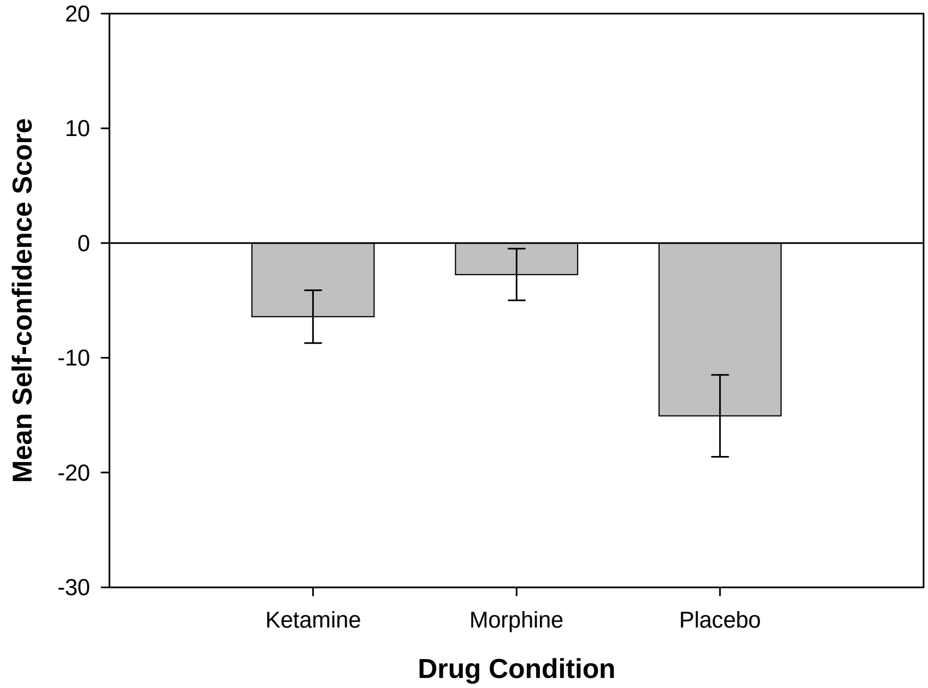


Figure 75. Mean self-confidence score by condition.

Table 33.
Results of paired comparison *t*-tests for self-confidence sub-scale scores (baseline adjusted).

Comparison	*p*
morphine vs. placebo	.052
morphine vs. ketamine	.008*
placebo vs. ketamine	.001*

* significant

There was no significant effect of *drug condition* on baseline-adjusted *need-for-control* scores, $F(2.53, 106.32) = 2.39$, $p = .083$, $\eta^2 = 0.054$, observed power = 0.54. However, the pattern of baseline adjusted responses is displayed in figure 76 which shows that the scores decreased from baseline in all three conditions.

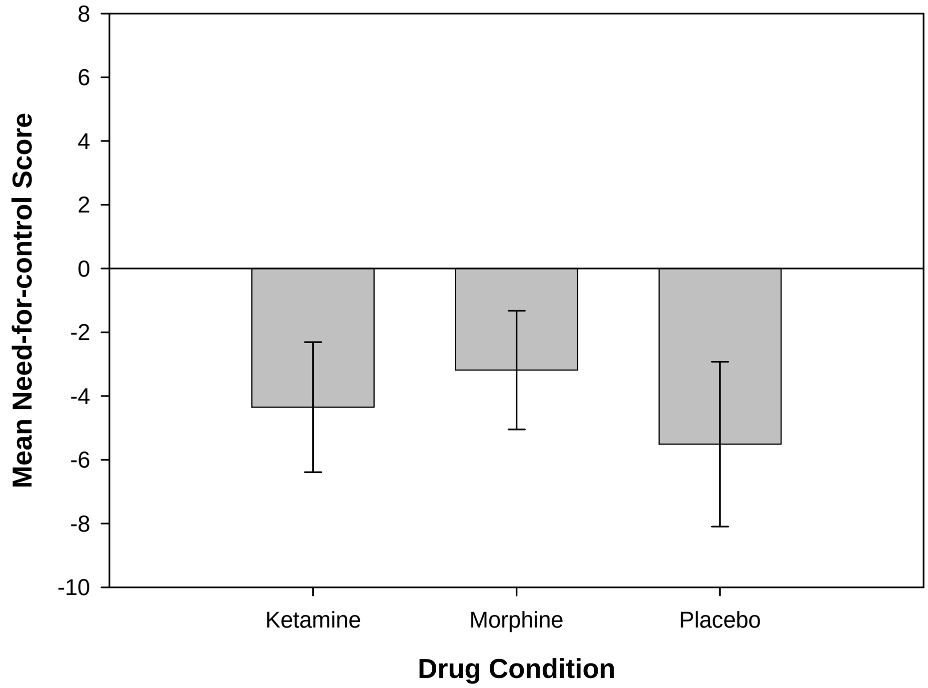


Figure 76. Mean need-for-control score by condition.

Finally, there was a significant effect of *drug condition* on baseline-adjusted total EVAR scores, $F(1.96, 82.45) = 11.04$, $p < .001$, $\eta^2 = 0.208$, observed power = 0.98 (figure 77). Subsequent paired comparison *t*-tests showed that in the ketamine condition, subjects' total risk propensity score decreased from baseline significantly more (thus a larger difference in scores) than in the morphine and placebo conditions (table 34). Also, in the morphine condition, baseline-adjusted scores decreased significantly more than in the placebo condition.

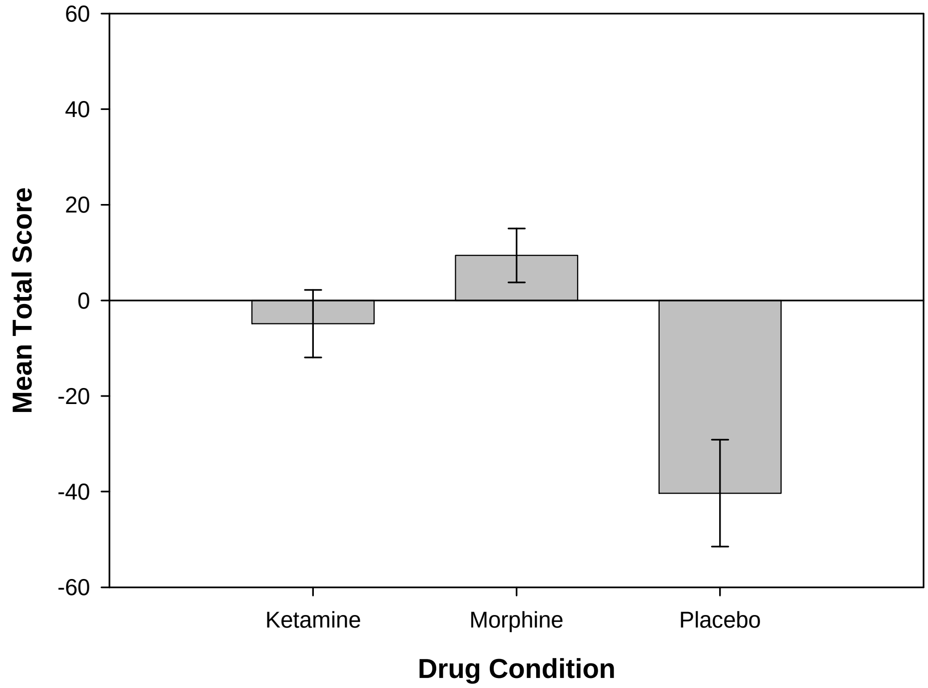


Figure 77. Mean total EVAR score by condition.

<u>Table 34.</u>

Results of paired comparison *t*-tests for total EVAR scores (baseline adjusted).

Comparison	*p*
morphine vs. placebo	.040*
morphine vs. ketamine	.003*
placebo vs. ketamine	< .001*

* significant

Discussion

This study was conducted in support of Combat Casualty Care research efforts investigating the feasibility of intranasal ketamine for acute battlefield analgesia. Specifically, it was conducted to characterize the effects of a single IM dose of 25 mg of ketamine (the bioequivalent dose of 60 mg of IN ketamine) versus the current analgesic standard of 10 mg of IM morphine (versus a placebo control) in the performance of representative military tasks in healthy Soldier volunteers. Study metrics included multiple-session vital signs and subjective symptom questionnaires, evaluation of risk propensity, and multiple Warrior Skill Tasks (outlined in table 7) tested for speed and accuracy. Note that some results, while statistically significant, are clinically or operationally unimportant (e.g., a performance time difference of tenths of a second or tenths of a degree Fahrenheit temperature difference). While these are duly presented in the Results section, they have been omitted from comment here.

Investigator observations

The rapid onset of ketamine was readily evident within minutes of injection for the vast majority of subjects, while the effects of morphine seemed to be more delayed and insidious. Not only was the time to effect faster for ketamine, but effects seemed to be much more precipitous. Often, minutes after injection, subjects would remark about the celerity of onset. The following quotation is representative: “Wow—that just hit me like a train!” Subjects subjectively reported noticeable ketamine drug effects at the +10 minute period without exception, while more than three-quarters reported continued effects at +40 minutes.

For the majority of subjects, the effects of ketamine were not unpleasant, and happiness/elation was the third most common symptom reported by overall frequency count for ketamine. Often subjects compared the feeling and symptoms to intoxication or feeling a “good buzz.” A minority was observed to be disconcerted by the effects; of those, anxiety or mild agitation seemed to predominate. For example, one mildly agitated subject became frustrated attempting to don the MOPP gear, and he threw the boots across the room complemented with a string of expletives. In all of these cases, the subjects maintained meaningful interaction with staff and responded to verbal reassurance when evaluated by the study physicians. There were no episodes of frank psychosis or requirement for any intervention (e.g., restraint or sedatives) beyond simple verbal reassurance. Subjects were frequently reminded of the voluntary nature of participation, but only one elected to briefly halt participation due to symptoms.

Data were collected on 48 subjects. One subject did not receive one of the three drug conditions due to a temporary contraindication discovered at that morning’s medical screening (an over-the-counter medication taken the previous night). One subject (mentioned at the end of previous paragraph) elected not to complete some warrior tasks after receiving ketamine due to severe dizziness, poor concentration, and perceptual distortions (“Everything is in slow motion.”). Symptoms rapidly improved by the +40 minute mark, and he was able to negotiate the remaining tasks (EST 2000).

An interesting observation was the repeated unsolicited subject comments regarding the ability to perform Soldier tasks despite the awareness of ketamine drug effect and perceived

impairment (see EVAR discussion later). Subjects seemed to be keenly aware of sensory distortions, cognitive slowing, and poor concentration, but seemed to perform many of the warrior tasks with little observed impairment. The following quotation is representative: “It was like I wasn’t all there, but when you said ‘go,’ my body just took over.” Perhaps this speaks to the beneficial aspects of training, particularly in tasks of automaticity and repetition (detail is provided below with respect to performance on specific Soldier tasks).

It is worth noting that emergency equipment, rescue medications, and EMS were not required at any time during the study. There were no serious adverse events. All subjects received post-study follow-up with one of the study physicians; no subject reported any lingering symptoms or effects.

Physiologic tests

Vital signs included systolic and diastolic blood pressure, pulse, oral temperature, respiratory rate, and room air pulse-oximetry measured pre-intervention (baseline), and at time sessions of 10 minutes, 40 minutes, 70 minutes, 4 hours, and 8 hours post-intervention. In addition to drug and time session, three different dosing times were analyzed (report times corresponding to red, yellow, and green colored t-shirt groups) including 0745 hours, 0900 hours, and 1015 hours. Report time did not yield significance, demonstrating consistency among the groups.

It is well-known that ketamine increases blood pressure, heart rate, and stroke volume while maintaining systemic resistance. Indeed, these properties are what make ketamine a good choice for the shocked patient (certain types of shock—hemorrhagic and septic, for example). This was evident in this investigation, as well. Ketamine resulted in higher systolic and diastolic pressures at 10 minutes (roughly 15%) and 40 minutes (roughly 5%, significance versus placebo only) after dosing. Likewise, ketamine resulted in a higher pulse at 10 minutes (roughly 15%). This was expected, and literature supports that these effects are mediated through increased plasma catecholamines—both increased release and reduced reuptake (e.g., Hersack, 1994). At the 10 minute period, a minority of subjects on ketamine did subjectively report racing heartbeat ($n = 3$) and/or pounding heartbeat ($n = 2$), as well as the 40 minute period ($n = 1$ and $n = 3$, respectively). However, these symptoms were not statistically significant by drug or by drug and session, and in no instance were these found to be of clinical significance by the study physicians.

The main effect of drug on respiratory rate and oxygen saturation was not significant. Ketamine does not produce significant ventilatory depression, even at higher doses. In spontaneously respiring patients, minute ventilation is maintained at similar levels to the awake state. Airway patency and preservation of pharyngeal and laryngeal reflexes are beneficial properties of the drug, though salivary and tracheobronchial secretions can increase. One subject subjectively reported this (excess salivation) at the 40 and 70 minute marks, though it was of no clinical consequence.

Regarding temperature, there was significance for overall time session with a slight dip at the four hour mark. This was not significant for drug condition, and possibly represents a change in rigorous activity level whereby subjects had completed testing and were convalescing with

minimal physical activity.

Questionnaires

Symptom questionnaire

The symptom checklist comprised 20 subjective measures listed in table 8 (as well as an open free-form) for time periods of pre-dose, +10 minutes, +40 minutes, +70 minutes, +4 hours, and +8 hours. Overall, the symptoms most often reported for ketamine included dizziness, poor concentration, and feelings of happiness compared with morphine which included tiredness, feelings of happiness, and nausea. Throughout, regardless of severity, subjects reported more symptoms while experiencing ketamine than with morphine or placebo.

Overall, by drug condition, significance testing demonstrated higher mean symptom scores for ketamine for nervousness, jitteriness, feelings of happiness/elation, dizziness, headache, double vision, blurred vision, disordered thought, poor concentration, and noticeable drug effect. All of these symptoms, with the exception of headache, were characterized by improvement (or stability in the case of nervousness and jitteriness) at the +40 minute mark and return or near return to baseline by the +70 minute mark. This is consistent with drug kinetics with a redistribution half-life of 11 minutes (note that termination of drug effect corresponds to redistribution). Mean headache scores for ketamine by time session trended upward over time, but the interaction between drug and time session was not statistically significant.

In instances of a significant interaction between drug condition and time session, post-hoc analysis with paired *t*-tests were conducted with a rigorous Bonferroni correction applied (5 time sessions x 3 drug conditions, $\alpha = .003$). Significance for ketamine was noted for jitteriness at +10 minutes, happiness/elation at +10 and +40 minutes, dizziness at +10, +40, and +70 minutes, double vision at +10 minutes, blurred vision at +10 and +40 minutes, disordered thought at +10 and +40 minutes, poor concentration at +10 and +40 minutes, and noticeable drug effect at +10, +40, and +70 minutes.

The subjective symptom scores for ketamine were not unexpected given known pharmacodynamics and side effect profile: increased pulse, blood pressure, and catecholamines, vestibular impairment, perceptual distortions, dissociative effects, nystagmus, euphoria, and others (see detail in Background section). And while the pharmacodynamic delineation of the drug is well-described in the literature, the study's main objective was to quantify performance effect for Warrior Skill Tasks.

Evaluation of Risks (EVAR) questionnaire

The results of the EVAR reveal differences between drug conditions that suggest applicable changes in behavior given one's condition. Specifically, in both the morphine and ketamine conditions, subjects showed a decrease in scores from baseline suggesting a tendency to become more conservative in behavior and less risk/thrill-seeking. This decrease was greater in the ketamine condition than in the morphine condition. This pattern of behavior was consistent across risk propensity factors, however, not significant for the *need-for-control* scores. It is probable that these results are a reflection of subjects' self-awareness of physical and

psychological state such that they recognize their impaired state and appropriately adjust their levels of acceptable risk.

Performance tests and Warrior Skill Tasks

Given that, overall, subjects reported more symptoms with ketamine than morphine and placebo, one might expect decrements in task performance in the form of more errors and increased performance time. Indeed, with significance demonstrated for symptoms of jitteriness, dizziness, double vision, blurred vision, disordered thought, and poor concentration within the first two symptom scoring sessions, it would be reasonable to expect subject difficulty with many aspects of the testing. However, decrements on ketamine, when present, were relatively underwhelming.

Engagement Skills Trainer (EST) 2000

Basic rifle marksmanship, arguably one of the most fundamental skills required of all Soldiers, failed to demonstrate significance for any shooting position (prone supported, prone unsupported, or kneeling) for any of the metrics (target hits, reaction time, CM shot distance, or RMS of aiming trace). This was particularly unexpected given the subjective symptoms of double and blurred vision, poor concentration, and disordered thought.

The results of the EST 2000 suggest that subjects' performance on the weapons simulator was unaffected by drug and do not support rejecting the null hypothesis. However, there are a number of factors to be considered in the interpretation of these results. First, 15 subjects' data were lost due to technical malfunction of the EST 2000, and 1 subject was excluded for medical reasons (missed dose). As reported, very small effect sizes were found as well as very low observed power values. One interpretation of these statistics is that the resulting sample of usable data was insufficient to detect a difference if one truly exists in the population. Not only would an increase in sample size increase statistical power but it would also narrow the confidence interval thus providing a better estimate of the true population value.

An alternative explanation is that these results do not rule out the null hypothesis and therefore support that there are no effects of ketamine (or morphine) on marksmanship performance. Preliminary evidence (Kelley, Athy, King, Erickson, 2010) suggests that visuo-spatial memory and ability play a role in marksmanship performance which are cognitive functions that have been shown to be unaffected by ketamine (Honey et al., 2003) thus supporting the lack of marksmanship impairment seen in this study. Likewise, previous studies have found that while recall memory, working memory and acquisition processes have been impaired by ketamine, recognition memory, a form of declarative memory, remains intact (Lofwall, Griffiths, & Mintzer, 2006). Recognition memory, one's ability to remember something that has previously been experienced, arguably has implications for performance on the weapons simulator, a familiar training scenario and thus may go unaffected by ketamine effects as seen in the results of this study. However, marksmanship is a learned skill which is considered procedural memory, an aspect of cognition which has not been explicitly tested with

ketamine. Therefore, further testing may be necessary to fully understand the relationship between marksmanship and ketamine.

It should be noted that previous research suggests that effects of ketamine on memory, behavior, and cognition are dose-dependent such that higher doses (e.g., 75 mg) produce impairments not seen in lower doses (Aubrun et al., 2007; Honey et al., 2003). The present study did not utilize multiple dosages, so potentially a larger dose may very well have produced impairments in marksmanship performance.

<u>Correct malfunctions of an M16 or M4 series rifle</u>

The SPORTS malfunction task consisted of six simple sequential steps to correct a stimulated weapon stoppage. Baseline corrected mean error rates and performance times failed to demonstrate significance by drug condition suggesting that acquired skill was unaffected by the administered drugs. In agreement with the results of marksmanship performance, it is reasonable to conclude that the procedural task was retained despite drug administration. However, caution must be taken in the interpretation of these results given that the Warrior Skill Tasks are not validated measures of cognitive function (see Limitations and Future considerations sections below).

<u>Don protective mask and MOPP</u>

Divided into two tasks consisting of donning, clearing, and checking the mask (task 1) and donning hood ensemble (task 2), the drug condition did not yield significance for accuracy for either task. Regarding performance times, significance was found for task 1 only. Yet, the consequence of this is unclear, however, given that subjects were slower on ketamine versus morphine, but not placebo. Furthermore, mean performance times were faster for all three drug conditions compared to baseline for task 2 suggesting continued learning.

Divided into four tasks corresponding with each of the MOPP postures, drug condition failed to demonstrate significance for accuracy for any of the four tasks. However, ketamine did significantly slow task performance time for all four tasks versus both morphine and placebo adding a mean total time of roughly 40 seconds. This task requires little cognitive ability or executive function, and this is most likely attributed to symptoms of dizziness, postural instability, and poor concentration. Indeed, many subjects were observed to sit on the floor to don MOPP trousers and boots, while they could easily balance on one leg upright at baseline (a few subjects actually fell over). Furthermore, as described with the EVAR discussion, subjects may have proceeded with slightly more caution armed with the awareness of their impaired state. Nonetheless, errors were not a consequence. The finding that performance speed was slowed but accuracy was spared is consistent with previous research (Honey, et al., 2003).

<u>Perform voice communications and request medical evacuation</u>

Radio assembly, voice communications, and the 9-line MEDEVAC tasks all failed to demonstrate significance for drug condition with the exception of task 2 of the MEDEVAC (lines 6-9). With respect to task 2, subjects on ketamine performed close to baseline for error and

performance time, but morphine and placebo groups performed better than baseline (fewer errors and faster) in both respects. This improvement again suggests task learning.

One particularly notable finding was the lack of significance for performance decrements on ketamine for task 1 (lines 1-5) of the MEDEVAC 9-line. Lines 1 through 5 include judgments and decisions regarding determination of pickup site, identifying patients by precedence, extracting frequencies and call signs, identifying requirement for special equipment, and others. Perhaps more so than any other task (shooting, donning mask and MOPP gear, immediate action malfunction drills, etc.), this task was judged to be the most complex with a wide margin for error. Subjects were required to analyze the scenario, extract pertinent information, make judgment and value determinations, and exhibit selective attention to only the relevant details. However, this task failed to demonstrate any significance among the drug groups.

Warrior Skill Tasks summary

Note that all subjects received training and repetitive testing to asymptote for tasks on the first day prior to baseline testing and dosing later in the week. Basic Soldier skill training, by design, is often repetitive in nature for skill acquisition and automaticity (especially desirable under extremely stressful or chaotic conditions such as combat). Despite the fact that subjects were more symptomatic on ketamine, the Warrior Skill Tasks were largely resistant to performance decrements suggesting that a trained task skill (the autonomous phase) is somewhat protected from the drugged state. And when decrements were present, they often manifested as slower performance times rather than procedural errors. This may represent a cautious state suggested by the EVAR whereby the subject is aware of impairment trading speed for preservation of accuracy.

Limitations

One obvious caveat to conclusions drawn from this study must be interpretation of results within the context of an absence of antecedent pain stimulus. As mentioned, the phenomenon of pain is quite complex, not limited to simple ascending neurosignaling pathways. It occurs within an entourage of a multitude of neurotransmitters, chemical mediators, and modulators. Indeed, a significant pain stimulus itself and/or the resulting physiologic milieu can most certainly affect Soldier performance.

With respect to pharmacokinetics, ketamine has high lipid solubility and low protein binding with a relatively fast onset of effect. The peak effect occurs in about five minutes following IM injection. Following this rapid onset, the effect is terminated largely by redistribution (approximate half-life 11 minutes) from the CNS to slower equilibrating tissues (Stevenson, 2005; Hersack, 1994). Note that task performance metrics in this study began immediately following the +10 minute symptom questionnaire. This was designed to allow time for IM absorption and an immediate close observation safety check of each subject by the study physicians. The result, however, is that testing likely began following at least one half-life of drug redistribution.

Results must also be interpreted within the context of subject sample representation of the

larger military force. For example, the average age of active duty officers and enlisted personnel within the DoD are 35 and 27 years, respectively (IOM, 2010), while the average study age of officers and enlisted subjects was essentially reversed at 28 and 35 years, respectively. Of the eight MOSs represented in the study population, five were aviation-related (not surprising given that the recruitment pool was from the Army Aviation Center of Excellence at Ft. Rucker). One may plausibly make the inference that this group represents a special subset of military forces, in general. Nonetheless, Warrior Tasks are not considered MOS-specific military skills and are universally trained to and required of all Soldiers.

Furthermore, with respect to study demographics, of military personnel serving in Operation Iraqi Freedom/Operation Enduring Freedom, 11% are female (IOM, 2010), while only 6% of the study subjects were female. Literature supports a higher incidence of psychomimetic reactions and emergence phenomenon in females (e.g., Annetta et al., 2005; Nicolaou, 2004), while other studies have failed to demonstrate a gender influence to drug response (e.g., Krystal et al., 1994). An often cited reservation for using ketamine is the tendency toward psychomimetic reactions or emergence phenomenon as the patient “reconnects” to sensory input. Incidence ranges widely in the literature (e.g., 5 to 30% according to Craven, 2007; Nicolaou, 2004). Much of the literature, however, is directed at anesthetic-level dosing, while our average dose was far below this (roughly 0.3 mg/kg). These reactions are reported to be more common in individuals with a psychiatric diagnosis or psychological susceptibility (e.g., Anneta et al., 2005). Note that the study population was screened for absence of this medical history. Furthermore, for safety reasons, a multitude of other medical conditions, some which may have increased the side effect profile or increased tendency toward complications, were also excluded.

As mentioned, the Warrior Skill Task training and repetitive testing to asymptote prior to the drugged conditions later in the week may have induced or reinforced the autonomous phase of skill acquisition for the Soldier tasks. This may have highlighted a relative resistance to performance decrements. Incorporating tests of basic cognitive function (e.g., working memory, acquisition process, higher order executive function) would help clarify the effects of the 25 mg ketamine and 10 mg morphine doses on these processes as they might relate to Soldier performance.

Conclusions

This study demonstrated many of the pharmacodynamic properties that make ketamine an attractive consideration for battlefield analgesia including rapid onset of action and hemodynamic stability. The 25 mg dose of ketamine did not result in elevated performance in Soldier tasks compared to 10 mg of morphine in healthy Soldier subjects. Overall, subjects reported more symptoms associated with ketamine versus morphine and placebo, chiefly among them dizziness, poor concentration, and feelings of happiness. Performance decrements on ketamine were demonstrated for some MOPP and 9-line MEDEVAC tasks, manifested as slower performance times rather than procedural errors. This may represent the adoption of a cautious posture suggested by the EVAR whereby the subject is aware of impairment trading speed for preservation of task accuracy. Despite the fact that subjects were more symptomatic on ketamine, the Warrior Skill Tasks were largely resistant to performance decrements suggesting that a trained task skill (autonomous phase) remains somewhat resilient to the drugged state at this dosage.

Future considerations

Ketamine will continue to have a prominent role in military medicine, as it has through military conflicts since the 1970's. Craven (2007) notes the advantages of hemodynamic stability, advantageous airway and respiratory properties, low cost, broad range of clinical applications, ease of storage, and excellent therapeutic index among others. Mercer (2009) goes as far as to call it the "drug of war."

Even if not found to be of value as a standalone analgesic or singular replacement/alternative for battlefield morphine, ketamine appears to have value as an opioid-sparing agent according to the literature. It possesses many desirable qualities (some confirmed in this study), and can conceivably serve as an opioid-sparring adjunct as part of a multi-modal approach for treating acute severe pain. Many authors have advocated that traumatic injuries necessitate such a multimodal approach for effective acute pain management (e.g., Buckenmaier, 2010). Furthermore, the IV and IM routes are notoriously problematic in the operational arena, and a simple intranasal delivery system could address many of these issues.

Another interesting potential exploit of ketamine is that of post-traumatic stress disorder (PTSD) mitigation. A recent study in 2008 at the Army's Institute of Surgical Research (ISR) noted that up to 17% of returning Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans report symptoms consistent with PTSD. In this study, burn patients receiving perioperative ketamine had a lower prevalence of PTSD compared to those who did not despite having larger burns, higher injury severity scores, undergoing more operations, and accruing more intensive care unit time (McGhee, Maani, Garza, Gaylord, and Black, 2008). The authors postulate better analgesia, neuronal protection, and the role NMDA receptor as potential explanations.

One notable area worth future development is the pharmacodynamic difference of the two enantiomers, S(+) and R(-). S(+) ketamine is noted to bear four times the affinity for the NMDA

receptor and also bind to μ and κ opioid receptors (Annetta, 2005). It's assayed to possess three times the anesthetic potency of the racemic mixture (Craven, 2007) while the R(-) is thought to be associated with some of the untoward side effects (Stevenson, 2005). With the potency of the S(+) enantiomer, lower doses could be employed for analgesia with fewer side effects.

Finally, the inclusion of Warrior Skill Tasks in this study provided a unique opportunity to assess performance on tasks specific and essential to Soldier performance and survivability. However if these tasks are to be employed in future research, it would be advantageous to assess their validity and reliability as measures of motor skill and cognitive performance. Further investigation of the cognitive processes underlying performance of these tasks will allow researchers to create stronger links between basic and applied background literature. This is important to accurately select tasks related to cognitive function specific to the research question at hand and to draw more specific conclusions and subsequently make more accurate recommendations.

References

American College of Surgeons, Committee on Trauma at http://www.facs.org/trauma/index.html (accesssed on 8 June 2010).

Annetta, M. G., Iemma, D., Garisto, C., Tafani, C., and Proietti, R. 2005. Ketamine: new indications for an old drug. Current Drug Targets. 6(7):789-794.

Anthony, D. 2006. EST 2000: Engagement Skills Trainer. Orlando: Cubic Defense Application.

Aroni, F., Iacovidou, N., Dontas, I., Pourzitaki, C., and Xanthos, T. 2009. Pharmacological aspects and potential new clinical applications of ketamine: Reevaluation of an old drug. Journal of Clinical Pharmacology. 49: 957-964.

Aubrun, F., Gaillat, C., Rosenthal, D., Dupuis, M., Motter, P., Marchetti, F., et al. 2007. Effect of low-dose ketatmine regimen on pain, mood, cognitive function and memory after major gynaecological surgery: A randomized, double-blind, placebo-controlled trial. European Journal of Anaesthesiology. 25: 97-105.

Bell, C. 2009. Intranasal Ketamine Product Review (Position Paper). U.S. Army Medical Materiel Development Activity, Medical Research and Materiel Command.

Bell, R. F., Dahl, J. B., Moore, R. A., and Kalso, E. 2005. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiologica Scandinavica. 49(10):1405-1428.

Bond, C. (Ed.). 2010. 68W Advanced Field Craft: Combat Medic Skills. Sudbury: Jones and Bartlett.

Bond, C. (Ed.). 2005. Combat Medic Field Reference. Sudbury: Jones and Bartlett.

Buckenmaier, CC. 2010. Military pain management in 21st century war. Military Medicine. 175 (7):7-12.

Clements, J. A., Nimmo, W. S., and Grant I. S. 1982. Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. Journal of Pharmaceutical Sciences. 71(5):539-542.

Combat Casualty Care Research Program at https://ccc.amedd.army.mil/index.jsp (accessed 7 June 2010).

Connor, D. J., Ralph, J. K., and Aldington, D. J. 2009. Field hospital analgesia. Journal of the Royal Army Medical Corps. 155(1): 49-55.

Couper, F. J., and Logan, B. K. 2004. Drugs and Human Performance Fact Sheets. Washington, DC: National Highway Traffic Safety Administration.

Craven, R. 2007. Ketamine. Anaesthesia. 62: 48-53.

Dale, O., Hjortkjaer, R., and Kharasch, E. D. 2002. Nasal administration of opioids for pain management in adults. Acta Anaesthesiologica Scandinavica. 46(7): 759-770.

Department of the Army. 2008a. Force Operating Capabilities. TRADOC PAM 525-66. Washington, DC.

Department of the Army, 2008b. Soldier's Manual of Common Tasks, Warrior Leader Skills Level 2, 3, and 4. Soldier Training Publication No. 21-24-SMCT. Washington, DC.

Department of the Army. 2006. Soldier's Manual of Common Tasks, Warrior Skills Level 1. Soldier Training Publication No. 21-1-SMCT. Washington, DC.

Dunn, B. Clinical pharmacist, Lyster Army Health Clinic (personal communication, 10 June 2010).

Finck, A. D, and Ngai, S. H. 1982. Opiate receptor mediation of ketamine analgesia. Anesthesiology. 56: 291-297.

Finn, J., Wright, J., Fong, J., MacKenzie, E., Wood, F., et al. 2004. A randomized crossover trial of patient controlled intranasal fentanyl and oral morphine for procedural wound care in adult patients with burns. Burns. 30(3): 262-268.

Galinski, M., Dolveck, F., Combes, X., Limoges, V., Smail, N., et al. 2007. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. American Journal of Emergency Medicine. 25(4):385-390.

Gaunt, C., Gill, J., and Aldington, D. 2009. British military use of morphine: A historical review. Journal of the Royal Army Medical Corps. 155(1): 46-48.

Glare, P. A., and Walsh, T. D. 1991. Clinical pharmacokinetics of morphine. Therapeutic Drug Monitoring. 13(1): 1-23.

Ghoneim, M. M., Hinrichs, J. V., Mewaldt, S. P., and Petersen, R. C. 1985. Ketamine: Behavioral effects of subanesthetic doses. Journal of Clinical Psychopharmacology. 5(2):70-77.

Grant, I. S., Nimmo, W. S., and Clements, J. A. 1981. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. British Journal of Anaesthesia. 53(8):805-810.

Guggenheim, K. Y. 1993. Paracelsus and the science of nutrition in the renaissance. Journal of Nutrition. 123(7): 1189-1194.

Hersack, R. A. 1994. Ketamine's psychological effects do not contraindicate its use based on a patient's occupation. Aviation, Space, and Environmental Medicine. 65: 1041-1046.

Honey, R. A. E, Turner, D. C, Honey, G. D, Sharar, S. R, Kumaran, D., Pomarol-Clotet, E., et al. 2003. Subdissociative dose ketamine produces a deficit in manipulation but not maintenance of the contents of working memory. Neuropsychopharmacology. 28: 2037-2044.

Hospira, Incorporated. 2004. Morphine Sulfate (package insert).

Hospira, Incorporated. 2005. Ketamine Hydrochloride (package insert).

Institute of Medicine. 2010. Returning Home from Iraq and Afghanistan: Preliminary Assessment of Readjustment Needs of Veterans, Service Members, and Their Families. Washington, DC: National Academy of Sciences.

Javelin Pharmaceuticals, "Ereska™ (intranasal ketamine)" at http://www.javelinpharmaceuticals.com/pmi150.html (accessed 11 June 2010).

Javelin Pharmaceuticals, "Javelin Pharmaceuticals Reports Ereska (Intranasal Ketamine) Phase III Trial Results in Postoperative Orthopedic Pain." Press release, 11 August 2009 at http://ir.javelinpharmaceuticals.com/releasedetail.cfm?ReleaseID=402643 (accessed 11 June 2010).

Javelin Pharmaceuticals, "Third Party Reexamination of Javelin Pharmaceuticals' Phase III Trial Data for Ereska (Intranasal Ketamine) Yields Statistically Significant Primary Endpoint." Press release, 11 February 2010 at http://ir.javelinpharmaceuticals.com/releasedetail.cfm?ReleaseID=444353 (accessed 11 June 2010).

Jolly, A. S., Jain, P., and Sood, J. 2007. Ketamine—Current uses and future perspectives. Journal of Anesthesia and Clinical Pharmacology. 23(2): 169-181.

Kelley, A. M., Athy, J. R., King M., and Erickson, B. 2010. Validation of the engagement skills trainer 2000 as a measure of cognitive performance. Technical report in preparation.

Killgore, W. D. S., Vo, A. H., Castro, C. A., and Hoge, C. W. 2006. Assessing risk propensity in American soldiers: Preliminary reliability and validity of the Evaluation of Risks (EVAR) scale –English version. Miliary Medicine. 171(3): 233-239.

Kollender, Y., Bickels, J., Stocki, D., Maruoani, N., Chazan, S., et al. 2008. Subanaesthetic ketamine spares postoperative morphine and controls pain better than standard morphine does alone in orthopaedic-oncological patients. European Journal of Cancer. 44(7):954-962.

Kotwal, R. S., O'Connor, K. C., Johnson, T. R., Mosely, D. S., Meyer, D. E., and Holcomb, J. B. 2004. A novel pain management strategy for Combat Casualty Care. Annals of Emergency Medicine. 44(2): 121-127.

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., et al.1994. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Archives of General Psychiatry. 51(3):199-214.

Lofwall, M. R., Griffiths, R. R., and Mintzer, M. Z. 2006. Cognitive and subjective acute dose effects of intramuscular ketamine in healthy adults. Experimental & Clinical Psychopharmacology. 14(4):439-449.

Maani, C. Chief of Anesthesia, US Army Institute of Surgical Research (personal communication, 4 December 2008)

McGhee, L. L., Maani, C V., Garza, T. H., Gaylord, K. M., and Black, I. H. 2008. The correlation between ketamine and posttraumatic stress disorder in burned service members. Journal of Trauma. 64(2): S195-S199.

Micromedex (Thomson Reuters) at http://www.thomsonhc.com (accessed 10 March 2010).

Mycek, M. J., Harvey, R. A., and Champe, P. C. (Eds.). 1997. Pharmacology, 2nd Edition. Philadelphia: Lippincott-Raven.

Nicolaou, D. D. 2004. Procedural sedation and analgesia. In Tintinalli, JE, Kelen, GD, Stapczynski, JS (Eds.), Emergency Medicine. New York: McGraw-Hill.

Paris, P. M., and Yealy, D. M. 2002. Pain Management. In Marx, JA, Hockberger, RS, Walls, RM (Eds.), *Rosen's* Emergency Medicine. St. Louis: Mosby.

Raj, N., Sehgal, A., Hall, J. E., Sharma, A., Murrin, K. R., and Groves, N. D. 2004. Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. European Journal of Anesthesiology. 21: 932-937.

Schmid, R. L., Sandler, A. N., and Katz, J. 1999. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 82(2): 111-25.

Sicard, B., Jouve, E., and Blin, O. 2001. Risk propensity assessment in military special operations. Military Medicine. 166(10): 871-874.

Smith, J. E., Russell, R., Mahoney, P. F., and Hodgetts, T. J. 2009. What is the ideal pre-hospital analgesic?—A questionnaire study. Journal of the Royal Army Medical Corps. 155(1): 44-46.

Stamatos, J. M., Boedeker, B. H., and Crowl, F. D. 1995. Perioperative Pain Management. In R Zajtchuk (Ed.), Anesthesia and Perioperative Care of the Combat Casualty (pp. 287-319). Washington, DC: Office of the Surgeon General.

Stevenson, C. 2005. Ketamine: A review. Update in Anaesthesia. 20: 25-29.

Subramaniam, K., Subramaniam, B., and Steinbrook, R. A. 2004. Ketamine as adjuvant analgesic to opioids: A quantitative and qualitative systematic review. Anesthesia & Analgesia. 99(2):482-495.

Tactical Combat Casualty Care Curriculum (updated 11 March 2010), U. S. Department of Defense Military Health System at http://www.health.mil/Education_And_Training/TCCC.aspx (accessed 7 June 2010).

Wedmore, I. S., Johnson, T., Czarnik, J., and Hendrix, S. 2005. Pain management in the wilderness and operational setting. Emergency Medicine Clinics of North America. 23: 585-601.

Wesensten, N. J. n.d. Cognitive and performance effects of intravenous administration of ketamine in normal, healthy volunteers. Walter Reed Army Institute of Research Report #1185.

Yanagihara, Y., Ohtani, M., Kariya, S., Uchino, K., Hiraishi, T., et al. 2003. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. Biopharmaceutics & Drug Disposition. 24(1):37-43.

Appendix A.

Medical exclusion criteria.

Subjects were excluded from the study for any of the following medical conditions:

- Previous allergic reactions to ketamine
- Previous allergic reactions to morphine or to narcotic medications
- Previous allergic reaction to latex
- HIV, Hepatitis B or C (acute state)
- COPD, asthma (acute or severe), sleep apnea, or active respiratory infection
- Tachycardia, heart murmur (other than functional or benign murmur), cardiovascular disease, or other cardiac disease (e.g. arrhythmia, valvular disease, cardiomyopathy)
- High blood pressure (>140/90) or history of hypertension
- Low blood pressure (<90/60)
- Active liver, thyroid, or kidney disease
- History of acute significant head injury, intracranial hemorrhage, stroke, or increased spinal fluid pressure
- Congenital brain malformation
- Epilepsy or seizure disorder (other than simple febrile seizures)
- Active gallbladder disease or gastrointestinal disorder (e.g. vomiting, constipation, diarrhea)
- Increased pressure in the eye(s) or glaucoma
- Addison's disease or other adrenal gland disorders
- History of enlarged prostate
- Serious psychological or psychiatric disorder, or use of psychotropic drugs
- History of drug abuse or addiction (including alcohol)
- Pregnant, breast feeding, or planning to become pregnant within a month of ending the study
- Use of the stimulant ephedra within the previous two years
- Concurrent use of medications contraindicated with the study drugs (outlined in table below)
- Recent drug therapy which, based on its known pharmacokinetics, will not have cleared from the body by 48 hours prior to participation (to be determined on a case-by-case basis depending on type of drug and when used)
- Other medical conditions (past or present) not listed above may entail exclusion from the study at the discretion of the examining study physician, depending on the severity of the condition and its impact upon subject and study safety

Drug interactions list (Epocrates® Online, 2 July 2009)

Ketamine Drug Interactions

- cocaine topical
- tramadol
- acetaminophen/tramadol
- aldesleukin
- hydrocodone/ibuprofen
- ibuprofen/oxycodone
- inhaled anesthetics
- levocetirizine
- memantine
- methadone
- mitotane
- morphine liposomal
- olopatadine nasal
- opiate agonist/antagonists
- opiates
- oxcarbazepine
- pramipexole
- promethazine/codeine
- ropinirole
- rotigotine transdermal
- rufinamide
- sedative/hypnotics
- tapentadol
- tetrabenazine
- topiramate

Morphine Sulfate Drug Interactions

- ethanol
- morphine liposomal
- tipranavir buprenorphine
- butorphanol
- butorphanol nasal
- nalbuphine
- pentazocine
- potassium salts
- sodium oxybate
- dofetilide
- metformin/sulfonylurea combos
- metformins
- pegvisomant
- sitagliptin/metformin
- opiate antagonists
- acetaminophen/butalbital
- acetaminophen/caffeine/CNS depressant combos
- acetaminophen/chlorpheniramine/dextromethorphan
- acetaminophen/chlorpheniramine/dextromethorphan/phenylephrine
- acetaminophen/chlorpheniramine/phenylephrine
- acetaminophen/codeine
- acetaminophen/diphenhydramine/phenylephrine
- acetaminophen/doxylamine/dextromethorphan
- acetaminophen/doxylamine/dextromethorphan/phenylephrine
- acetaminophen/doxylamine/dextromethorphan/pseudoephedrine
- acetaminophen/doxylamine/phenylephrine
- acetaminophen/hydrocodone
- acetaminophen/oxycodone
- acetaminophen/pheniramine/phenylephrine
- acetaminophen/propoxyphene
- acetaminophen/tramadol
- albuterol/ipratropium inhaled
- aldesleukin
- combos
- azelastine nasal
- baclofen
- baclofen intrathecal
- barbiturates
- brompheniramine/dextromethorphan/phenylephrine
- brompheniramine/dextromethorphan/pseudoephedrine
- BZDs, all
- cannabinoids
- carisoprodol
- central alpha 2 agonists
- cetirizine
- cetirizine/pseudoephedrine
- chlorpheniramine/dextromethorphan
- chlorpheniramine/dextromethorphan/phenylephrine
- chlorpheniramine/dextromethorphan/pseudoephedrine
- chlorpheniramine/hydrocodone
- chlorzoxazone
- clozapine
- cyclobenzaprine
- cyclopentolate/phenylephrine ophthalmic
- dantrolene
- darifenacin
- dexmedetomidine
- disopyramide
- doxazosin
- doxylamine/dextromethorphan
- droperidol
- efavirenz/emtricitabine/tenofovir
- emtricitabine/tenofovir ethosuximide
- etomidate
- gabapentin
- haloperidol
- hydrocodone/ibuprofen
- ibuprofen/oxycodone
- inhaled anesthetics
- ketamine
- levocetirizine
- local anesthetics local anesthetics/epinephrine
- loperamide
- loxapine
- meprobamate
- metaxalone
- methocarbamol
- metoclopramide
- mitotane
- molindone
- olanzapine olanzapine/fluoxetine
- olopatadine nasal
- opiates
- orphenadrine
- oxcarbazepine

Morphine Sulfate Drug Interactions (continued)

- paliperidone
- pheniramine/dextrome-thorphan/phenylephrine
- phenothiazines
- pimozide
- pramipexole
- pregabalin
- promethazine/codeine
- propofol
- propoxyphene
- pyridostigmine
- quetiapine
- risperidone
- ropinirole
- rotigotine transdermal
- rufinamide
- sedative/hypnotics
- solifenacin
- succinylcholine
- tapentadol
- tenofovir
- tetrabenazine
- thalidomide
- thiothixene
- tiagabine
- tizanidine
- topiramate
- tiagabine
- tizanidine
- topiramate
- tramadol
- tricyclic antidepressants
- valproic acid derivatives
- ziconotide intrathecal
- ziprasidone
- zonisamide

Other potential exclusionary criteria (at the discretion of the examining physician) included:

- Previous adverse reactions to analgesics or anesthetics
- History of bowel obstruction or other constipation or colo-rectal problems
- History of liver, thyroid dysfunction or kidney disease
- Previous head trauma or injury
- Previous eye injury
- Recent history of problems urinating
- Immunologic Dysfunction
- Cancer
- Asthma or breathing disorder

<u>Appendix B.</u>

<u>Open-ended subject comments on symptom checklist.</u>

Drug	Session	Comment	*n*
Ketamine	pre-dose	(None)	
	+10 minutes	Drunk/tipsy/intoxicated	12
		Dry mouth	1
		Numbness/tingling	8
		Weird taste/metallic taste	3
		Clammy/sweaty	9
		Disconnected/detached	5
		Lightheaded	1
		Floating/weightless sensation	1
		Slow movement	3
		Delayed/slow vision	4
		Balance/equilibrium is off	3
		Delayed/feeling slow motion	3
		Euphoria	2
		Sensitive touch (weird)	1
		Moving weird	1
		Feel stunned	1
		Can't remember	1
		Disoriented	1
		Paranoid	1
		Seems busy; lots of things going on, noises louder	1
		Very light	1
		Feeling hot	1
		Wobbley	1
		Hard time focusing	1
		Spacey	1
		Weird	1
		Ear ringing	1
		Relaxed	1
		Difficult to focus at distance	1
		Loopy	1
		Warm	1
		Hard to read	1
		Feel combat ineffective	1

Drug	Session	Comment	*n*
Ketamine	+40 minutes	Drunk	2
		Dry mouth	1
		Numbness/tingling	6
		Weird taste	1
		Sweaty/clammy	5
		Disconnected/detached	3
		Sore at injection site	1
		Floating/weightless sensation	3
		Slow movement	1
		Delayed/slow vision	1
		Balance/Equilibrium is off	1
		Delayed/feeling slow motion	2
		Time Distortion	3
		Euphoria	1
		Chills	1
		Off a little bit	1
		Lungs feel clear	1
		Apathetic	1
		Paranoia	1
		Cold hands	1
		Faster thinking	1
		Feels like I worked out, muscular weakness	1
		Feel gassy	1
		Extra salivation	1
	+70 minutes	Numbness	2
		Weird taste/metallic taste	2
		Disconnected/detached	2
		Sore at injection site	1
		Floating/weightless sensation	2
		Delayed/feeling slow motion	3
		Calm	2
		Breathing was different	1
		Extra salivation	1
		Mucous buildup	1
		Feel hungover	1
	+4 hours	Floating/weightless sensation	1
		Delayed/feeling slow motion	1
	+8 hours	(None)	

Drug	Session	Comment	*n*
Morphine	pre-dose	Stuffy nose	1
	+10 minutes	Feel lightly buzzed	1
		Sore/muscle pain at injection site	4
		Lightheaded	1
		Floating/weightless sensation	1
		Stuffy nose	1
		Balance off	1
		Delayed/feeling slow motion	1
		Calm	1
		Charlie Horse cramp	1
		Warm chest pressure	1
		Stomach tightness	1
		Feels like rock in my stomach	1
	+40 minutes	Drunk/tipsy	3
		Dry mouth	1
		Tingling	2
		Sore at injection site	1
		Lightheaded	2
		Floating/weightless sensation	3
		Stuffy nose	1
		Balance problems/balance off	2
		Delayed/feeling slow motion	1
		Calm	1
		Uncoordinated	2
		Stomach unsettled	1
		Medicine head	1
		Warm fuzzies	1
		Flushed	1
		More sensitive to color after shooting	1
		Stomach tightness	1
		Ansy	1
		Warm chest pressure	1
		Heavy feet	1
		Flush	1
		Impaired	1

Drug	Session	Comment	*n*
Morphine	+70 minutes	Drunk/beer buzz	2
		Dry mouth/cotton mouth	3
		Lightheaded	2
		Floating/weightless sensation	2
		Stuffy nose	1
		Balance problems/balance off	3
		Delayed/feeling slow motion	1
		Calm	1
		Uncoordinated	1
		Medicine head	1
		Lost appetite	1
		Relaxed	1
		Shaking	1
		Heavy extremities	1
		Flushed	1
	+4 hours	Drunk	1
		Stuffy nose	1
		Balance issues	1
		Thick saliva	1
	+8 hours	(None)	
Placebo	pre-dose	Stuffy nose	1
	+10 minutes	Stuffy nose	1
	+40 minutes	Stuffy nose	1
		Delayed/feeling slow motion	1
		Weakness in arms	1
	+70 minutes	Stuffy nose	1
		Delayed/feeling slow motion	1
		Weakness in arms	1
	+4 hours	Stuffy nose	1
	+8 hours	Stuffy nose	1

Appendix C.

Significant results summary table.

	MEASURE	DRUG	TIME SESSION	DRUG AND TIME SESSION
Physiologic Tests				
Vital Signs	Systolic blood pressure	p<.001	p<.001	p<.001
	Diastolic blood pressure	p=.001	p<.001	p=.002
	Pulse	p=.001	p<.001	p<.001
	Temperature	NS	p=.004	p=.021
	Respiration rate	NS	NS	NS
	Oxygen saturation	NS	p<.001	NS
Questionnaires				
Symptom Questionnaire	Nervousness	p=.020	p<.001	NS
	Feelings of excitement	NS	p<.001	p<.001
	Jitteriness	p=.002	p=.001	p=.002
	Feelings of aggression	NS	NS	NS
	Feelings of happiness/elation	p<.001	p<.001	p<.001
	Tiredness	NS	p<.001	p=.021
	Dizziness	p<.001	p<.001	p<.001
	Racing heartbeat	NS	NS	NS
	Pounding heart or heartbeat	NS	p=.027	NS
	Headache	p=.049	NS	NS
	Nausea	NS	NS	p<.001
	Vomiting	NS	NS	p=.048
	Tremor	NS	NS	NS
	Double vision	p<.001	p<.001	p<.001
	Blurred vision	p<.001	p<.001	p<.001
	Itching	p=.016	NS	NS
	Disordered thought process	p<.001	p<.001	p<.001
	Poor concentration	p<.001	p<.001	p<.001
	Unreal thoughts	NS	NS	NS
	Any noticeable drug effect	p<.001	p<.001	p<.001
EVAR	Risk	p<.001	--	--
	Confidence	p=.001	--	--
	Control	NS	--	--
	Total	p<.001	--	--

NS = not significant

Significant results summary table (continued).

	MEASURE	DRUG	TIME SESSION	DRUG AND TIME SESSION
Performance Tests/Warrior Skill Tasks				
Engage Targets with M16 or M4 Rifle (prone supported)	Accuracy/hits	NS	--	--
	Reaction time	NS	--	--
	Shot radius	NS	--	--
	Aim trace	NS	--	--
Engage Targets with M16 or M4 Rifle (prone unsupported)	Accuracy/hits	NS	--	--
	Reaction time	NS	--	--
	Shot radius	NS	--	--
	Aim trace	NS	--	--
Engage Targets with M16 or M4 Rifle (kneeling)	Accuracy/hits	NS	--	--
	Reaction time	NS	--	--
	Shot radius	NS	--	--
	Aim trace	NS	--	--
Shoot—Don't Shoot IFF (9-mm pistol)	Accuracy/hits	NS	--	--
	Reaction time	NS	--	--
	Shot radius	NS	--	--
	Aim trace	NS	--	--
Correct Malfunctions (SPORTS)	Accuracy	NS	--	--
	Performance time	NS	--	--
Don ProMask (mask, task 1)	Accuracy	NS	--	--
	Performance time	$p=.032$	--	--
Don ProMask (hood, task 2)	Accuracy	NS	--	--
	Performance time	NS	--	--
Don MOPP (MOPP 1, task 1)	Accuracy	NS	--	--
	Performance time	$p<.001$	--	--
Don MOPP (MOPP 2, task 2)	Accuracy	NS	--	--
	Performance time	$p<.001$	--	--
Don MOPP (MOPP 3, task 3)	Accuracy	NS	--	--
	Performance time	$p<.001$	--	--
Don MOPP (MOPP 4, task 4)	Accuracy	NS	--	--
	Performance time	$p<.001$	--	--

NS = not significant

Significant results summary table (continued).

	MEASURE	DRUG	TIME SESSION	DRUG AND TIME SESSION
Performance Tests/Warrior Skill Tasks				
Perform Voice Communications/Radio Task	Accuracy	NS	--	--
	Performance time	NS	--	--
Request MEDEVAC (lines 1-5, task 1)	Accuracy	NS	--	--
	Performance time	NS	--	--
Request MEDEVAC (lines 6-9, task 2)	Accuracy	p=.026	--	--
	Performance time	p=.006	--	--

NS = not significant

Acronyms

AAR	after action review
ACLS	Advanced Cardiac Life Support
ACS	American College of Surgeons
AED	Automatic External Defibrillator
ANOVA	analysis of variance
BART	Balloon Analogue Risk Task
BBB	blood-brain barrier
BCE	Biber Cognitive Estimation
BLS	Basic Life Support
BMI	Body Mass Index (kg/m^2)
BRM	Basic Rifle Marksmanship
CADSS	Clinician Administered Dissociative State Scale
CB	Chemical and Biological
CBRN	Chemical, Biological, Radiological, and Nuclear
CCCRP	Combat Casualty Care Research Program
CM	center of mass
CVLT	California Verbal Learning Task
CYP450	Cytochrome P450
DoD	Department of Defense
DOT	Design Organization Task
EMS	Emergency Medical Services
EST	Engagement Skills Trainer
EVAR	Evaluation of Risks
GPT	Grooved Pegboard Test
IFF	Identify Friend or Foe
IM	intramuscular
IN	intranasal
IOM	Institute of Medicine
IPT	Integrated Product Team
IV	intravenous
IVI	intravenous infusion
kg	kilogram
LAHC	Lyster Army Health Clinic
MANOVA	multivariate analysis of variance
MEDEVAC	medical evacuation
mg	milligram
mL	milliliter
MOPP	Mission-Oriented Protective Posture
MOS	Military Occupational Specialties
MRMC	Medical Research and Materiel Command
ng	nanogram
NMDA	N-methyl-D-aspartate
PEDT	Pennsylvania (University of) Emotion Differentiation Test

PRM	Pattern Recognition Memory
PTSD	post-traumatic stress disorder
PVT	Psychomotor Vigilance Task
RMS	root mean square
RVIP	Rapid Visual Information Processing
SC	symptom checklist
SPID-6	Sum of Pain Intensity Differences over 0-6 hours
SPORTS	Slap; Pull; Observe; Release; Tap; Squeeze
SWM	Spacial Working Memory
TCCC or TC3	Tactical Combat Casualty Care
TOL	Tower of London
USAARL	U.S. Army Aeromedical Research Laboratory
USAMMDA	U.S. Army Medical Materiel Development Activity
WCST	Wisconsin Card Sort Task
WLMR	Wechsler Logical Memory Recall Test
WRAIR	Walter Reed Army Institute of Research

Department of the Army
U.S. Army Aeromedical Research Laboratory
Fort Rucker, Alabama, 36362-0577
www.usaarl.army.mil

U.S. Army Medical Research and Materiel Command